Official Study Title: A Phase II Trial of Surgery and Fractionated Re-Irradiation for Recurrent Ependymoma

CTG Number: NCT02125786

Document Date: 2/1/2023

St. Jude
RERTEP
Initial version, dated: 12/10/2013 Resubmitted to IRB: 3/17/2014 (IRB Approved: 3/18/2014)
Activated: 04/21/2014
Rev 0.1, dated: September 3, 2015 (IRB Approved: 10/22/2015) Activated: November 2, 2015
Amend 1.0, dated: September 1, 2016 (IRB Approved: 12/06/2016) Activated: December 14, 2016
Rev. 1.1 dated: July 28, 2017 (IRB Approved: 8/30/2017) Activated: September 7, 2017
Amend 2.0, dated: January 11, 2019 (IRB Approved 08-09-2019 Activated: August 19, 2019
Amend 3.0 dated: June 30, 2020 (IRB Approved: 08-11-2020) Activated: September 20, 2020
Rev. 3.1, dated: September 14, 2020 (IRB Approved: 10-27-2020) Activated:November 11, 2020
Rev. 3.2, dated January 19, 2023 (IRB Approved 02-01-2023)Activated: February 28, 2023

A PHASE II TRIAL OF SURGERY AND FRACTIONATED RE-IRRADIATION FOR RECURRENT EPENDYMOMA
IND #104987

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Protocol Summary

Protocol MNEMONIC and Title: RERTEP - A Phase II Trial of Surgery and Fractionated Re-irradiation for Recurrent Ependymoma
Principal Investigator: Thomas E. Merchant, DO, PhD
IND Holder: ^{11}C-methionine, IND 104987, Sponsor of IND: St. Jude Children's Research Hospital
Brief Overview: There is a need to determine the role of re-irradiation in patients with recurrent ependymoma after prior therapy that includes fractionated radiation therapy administered with curative intent. Outcomes reported from St. Jude Children's Research Hospital suggest that a proportion of children with recurrent ependymoma after prior irradiation may be successfully treated with additional surgery and a second course of irradiation; however, there are a number of unanswered questions about this approach including portability, morbidity and mortality, and the biological basis for success. Responding to these questions requires prospective study of outcomes and tumor biology.
Intervention: Neurosurgery and fractionated irradiation.
Brief Outline of Treatment Plan: The goal of this study is to determine the feasibility and safety of treating recurrent ependymoma with a second course of irradiation using cumulative doses that exceed those used in routine clinical practice. Surgery is an important part of this study and will be used to document recurrent ependymoma and reduce the tumor burden when feasible. Patients with local failure after prior surgery and focal irradiation will undergo surgery and focal re-irradiation; however, those age > 3 years with tumors having 1q gain will be offered craniospinal irradiation. Those with metastatic disease limited to the neuraxis will receive craniospinal irradiation after surgery. Patients with combined local and distant failure will be treated with surgery and craniospinal irradiation. Patients will be stratified for outcome according to diagnosis and prior therapy. All patients will be evaluated for the effects of the treatment regimen.

Primary Objective:

1.1 To estimate the progression-free and overall survival distributions for children and young adults with recurrent ependymoma treated with a second course of irradiation while monitoring for excessive central nervous system necrosis.

Responsible Investigator: Thomas E. Merchant
Biostatistician: Yimei Li and Shengjie Wu
Estimated date for completion of data collection: 10-11 years after activation.

Secondary and Exploratory Objectives:

1.2 To explore potential associations of clinical and treatment factors with the incidence and severity of neurological, endocrine and cognitive deficits in children and young adults with ependymoma treated with a second course of irradiation.

Responsible Investigators: Heather M. Conklin and Thomas E. Merchant
Biostatisticians: Hui Zhang and Shengjie Wu
Estimated date for completion of data collection: 10-11 years after activation.

1.3 Using specific measures of sleep quality, excessive daytime sleepiness, daytime activity, fatigue, symptom distress, and quality of life, explore associations of sleep, fatigue and quality of life with other measures of CNS effects, clinical and treatment factors in children and young adults with ependymoma treated with a second course of irradiation.

Responsible Investigator: Belinda Mandrell
Biostatisticians: Hui Zhang
Estimated date for completion of data collection: 10-11 years after activation.

1.4 To describe physical performance and movement in children, adolescents and young adults with ependymoma treated with a second course of irradiation.

Responsible Investigator: Kirsten Ness
Biostatisticians: Yimei Li
Estimated date for completion of data collection: 10-11 years after activation.

1.5 Estimate and compare the response of recurrent tumor and the incidence and severity of macrostructural, microstructural, physiologic and vascular effects on brain tissue in children and young adults with ependymoma after treatment with a second course of irradiation using specific methods of diffusion, contrast-enhancement, magnetization transfer, vascular neuroimaging, and explore the association between these and other measures of CNS effects and clinical and treatment factors.

Responsible Investigators: Julie Harreld and Chia-ho Hua

Biostatisticians: Yimei Li
Estimated date for completion of data collection: 10-11 years after activation.

1.6 Estimate the avidity of ependymoma to ^{18}F-fluorodeoxyglucose (FDG) and ^{11}C-methionine positron emission tomography (IND # 104987) prior to radiation therapy and correlate change in avidity 12, 24 and 36 months after a second course of irradiation with tumor progression.

Responsible Investigator: Barry Shulkin
Biostatisticians: Yimei Li
Estimated date for completion of data collection: 10-11 years after activation.

1.7 Measure growth factor and cytokine responses in children and young adults with ependymoma after treatment with a second course of irradiation, and explore associations between these and other measures of CNS effects and clinical and treatment factors. Descriptively compare findings to similar growth factors and cytokines evaluated in historic patients during their initial course of irradiation.

Responsible Investigator: Thomas E. Merchant
Biostatistician: Yimei Li
Estimated date for completion of data collection: 10-11 years after activation.

1.8 Conduct molecular analyses on tumor samples (and blood where a germline control is required) with the aim of studying associations between tumor molecular subgroup and treatment response and various side effects, including vasculopathy, hearing loss, cognitive deficits, growth hormone deficiency, and other measures as appropriate.

Responsible Investigator: David Ellison
Biostatistician: Yimei Li
Estimated date for completion of data collection: 10-11 years after activation.

1.9 To explore the association of chemotherapy given prior to re-irradiation with PFS and OS distributions.

Responsible Investigator: Thomas E. Merchant
Biostatistician: Yimei Li
Estimated date for completion of data collection: 10-11 years after activation.

Hypotheses:

1.1.1 Hypothesis for Primary Objective – Ependymoma recurrent after prior therapy that included irradiation is genetically distinct from the untreated tumor. The effectiveness of a second course of irradiation depends on tumor biology and the pattern of initial tumor progression.

1.1.2 Hypothesis for Secondary Objective - A second course of irradiation may be safely administered to patients with recurrent ependymoma after prior irradiation. The incidence and severity of side effects after second irradiation correlate with relevant clinical factors and treatment parameters, including radiation dose to normal tissue volumes. The selection of patients for re-irradiation can be improved by models that include clinical and treatment factors and longitudinal measures of CNS effects.

Criteria for Evaluation: Disease control will be evaluated using MR imaging performed during regular intervals after enrollment. Patients will be considered to have progressive disease when there is progressive growth of any component of the tumor based on serial imaging.

Study Design: Phase II study assessing the rate of failure for patients with ependymoma treated with surgery and a second course of irradiation.

Inclusion Criteria:

1. Progressive intracranial ependymoma after prior focal irradiation
2. Patients aged 1-21 years at the time of enrollment
3. Adequate performance status (ECOG < 3) and research participant does not require mechanical ventilation
4. Interval from start of initial radiation therapy to enrollment > 9 months

Exclusion Criteria:

1. Prior craniospinal irradiation
2. Pregnant women are excluded from this study because radiation therapy is an agent with the potential for teratogenic or abortifacient effects.
3. Any patient with both metastatic ependymoma and age <3 years at the time of enrollment.

Sample Size: Accounting for ineligible patients, the total number of patients to be accrued to this study is estimated to be 99. We expect to enroll about 12 patients per year for a period of 8-9 years.

Randomization: N/A

Data Analyses:

Primary Aim:

To estimate the progression-free and overall survival distributions for children and young adults with recurrent ependymoma treated with a second course of irradiation while monitoring for excessive central nervous system necrosis.

Secondary Aims:

Evaluate functional outcomes and host and tumor biology in patients with recurrent ependymoma treated with a second course of irradiation.

Primary Anticipated Completion Date: May, 2023

Anticipated Study Completion Date: May, 2028

Timeframe for Primary Outcome Measure: Five years after last patient has been enrolled.

Data Management: Data management will be provided by the clinical research staff in the Department of Radiation Oncology at St. Jude Children's Research Hospital and all data will be entered and maintained in the St. Jude CRIS database.
Human Subjects: The risks to subjects treated with surgery and re-irradiation are expected to be higher when compared to initial surgery and radiation therapy. Patients previously treated with surgery and radiation therapy have accepted the burden of risk associated with those treatments including neurological, endocrine, cognitive and somatic dysfunction. We estimate that these risks will be magnified depending on whether the volume for the second course of irradiation is limited to the primary tumor bed or craniospinal. The effects of craniospinal irradiation are known to be largely dependent on age at the time of treatment. Regardless of treatment approach, the short term side effects may include nausea, vomiting, fatigue, loss of appetite, hair loss and headache. Common late effects include hormone deficiencies and weight gain, fatigue and sleep disorders, cognitive effects (memory, attention, behavior, learning, global intelligence), headache and permanent hair loss. Less common late effects are secondary tumor formation (benign or malignant), vasculopathy and stroke, neurological effects such as hearing loss, vision loss and seizures, and structural effects such as necrosis or myelopathy that may lead to permanent disability or death. Patients will be informed of this and other possible side effects during informed consent. Adverse events will be monitored, reported, and treated appropriately. The risks to subjects may be increased from surgery include all of the side effects listed above in addition to delayed wound healing, infection and stroke. The use of chemotherapy at any time may increase the side effects of re-irradiation.

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1.0 OBJECTIVES

1.1 Primary Hypothesis and Objective

Hypothesis: Ependymoma recurrent after prior therapy that included irradiation is genetically distinct from the untreated tumor. The effectiveness of a second course of irradiation depends on tumor biology and the pattern of initial tumor progression.

1.1.1 To prospectively estimate the progression-free and overall survival distributions for children and young adults with recurrent ependymoma treated with a second course of irradiation while monitoring for excessive central nervous system necrosis.

1.2 Secondary Hypotheses and Secondary Objectives

Hypotheses: A second course of irradiation may be safely administered to patients with recurrent ependymoma after prior irradiation. The incidence and severity of side effects after second irradiation correlate with relevant clinical factors and treatment parameters, including radiation dose to normal tissue volumes and the use of chemotherapy before or after second irradiation. The selection of patients for re-irradiation can be improved by models that include clinical and treatment factors and longitudinal measures of CNS effects.

1.2.1 To explore potential associations of clinical and treatment factors with the incidence and severity of neurological, endocrine and cognitive deficits in children and young adults with ependymoma treated with a second course of irradiation.

1.2.2 Using specific measures of sleep quality, excessive daytime sleepiness, daytime activity, fatigue, symptom distress, and quality of life, explore associations of sleep, fatigue and quality of life with other measures of CNS effects, clinical and treatment factors in children and young adults with ependymoma treated with a second course of irradiation.

1.2.3 To evaluate and explore differences in physical performance and movement in children and young adults with ependymoma treated with a second course of irradiation.

1.2.4 Estimate and compare the response of residual tumor and the incidence and severity of structural, physiological, and vascular effects of normal brain in children and young adults with ependymoma after treatment with a second course of irradiation using specific methods of diffusion, contrast-enhancement, magnetization transfer, vascular and functional

neuroimaging, and explore the association between these and other measures of CNS effects and clinical and treatment factors. Determine the time course of gray matter and white matter tract injury and recovery post irradiation and the association between imaging metrics derived from serial quantitative neural imaging and radiation dosimetry as well as neuro-cognitive outcomes.

1.3 Exploratory Objectives

1.3.1 Estimate the avidity of ependymoma to ^{18}F-fluorodeoxyglucose (FDG) and ^{11}C-methionine positron emission tomography (IND # 104987) prior to radiation therapy and correlate change in avidity 12, 24 and 36 months after a second course of irradiation with tumor progression.

1.3.2 Measure growth factor and cytokine responses in children and young adults with ependymoma after treatment with a second course of irradiation, and explore associations between these and other measures of CNS effects and clinical and treatment factors. Descriptively compare findings for patients treated with an initial course of irradiation.

1.3.3 To conduct a variety of exploratory molecular analyses on tumor samples (and blood where a germline control is required), including but not limited to broad (genome-wide / array-based) or focused (gene-specific) analyses at the DNA, RNA, or protein level and next generation (whole genome, exome, transcriptome) sequencing in an effort to improve our understanding of ependymoma biology, and to explore associations between molecular findings and treatment response and various side effects including vasculopathy, hearing loss, cognitive deficits, and growth hormone deficiency and other measures as appropriate.

1.3.4 To explore the association of chemotherapy given prior to re-irradiation with progression-free survival and overall survival distributions.

1.3.5 To compare the progression-free and overall survival distributions for children (age > 3 years) and young adults with recurrent ependymoma and 1q gain treated with a second course of irradiation (focal or craniospinal) while monitoring for excessive central nervous system necrosis.

1.4 Definitions

1.4.1 Clinical factors include but are not limited to vital statistics, auxological measures and tumor variables that uniquely identify the patient and the natural history of their disease. Clinical factors also include laboratory measures of host and tumor biology and response to treatment.

1.4.2 Treatment factors include but are not limited to type and extent of surgical interventions including operative complications. Treatment factors also include the full extent of radiation therapy treatment planning and delivery parameters and chemotherapy before or after radiation therapy.

1.4.3 Measures of CNS effects refers to the broad categories of different objective clinical or laboratory methods used to evaluate the acute and late effects of radical surgery or limited surgery and radiation therapy in this protocol (neuropsychological, growth factor and cytokines, endocrine, physical performance and movement, host and tumor genetics, structural, functional and vascular imaging, audiology, neurology and ophthalmology, sleep, fatigue and quality of life, and positron emission tomography). Each of these categories includes smaller or more specific measures. Some of these measures may be used to evaluate tumor response to treatment (cytokines, tumor and host genomics and neuroimaging).

2.0 BACKGROUND AND RATIONALE

2.1 Problem Definition

Children with ependymoma who experience disease progression after surgery and radiation therapy have few options: chemotherapy may prolong survival but is not curative and surgeons are reluctant to approach recurrent disease without effective adjuvant therapy. Fractionated re-irradiation may be a potential treatment for these patients; however, guidelines have not been established, relative benefits and risks are unknown, a most reported series include diverse diagnoses and combine adult and pediatric patients [1, 2]. Single fraction radiosurgery has been used in selected cases of locally recurrent or metastatic ependymoma with mixed results: morbidity has been high and durable disease control has not been clearly demonstrated [3, 4]. Fractionated re-irradiation has not been systematically explored for ependymoma mainly because it affects the very young and pediatric oncologists are not familiar with re-irradiation as a treatment option. In this study, we propose to irradiate children with ependymoma that is recurrent after prior fractionated focal irradiation and to investigate clinical and biologic features that may be associated with subsequent disease control and toxicity.

The rationale for this study is based on the St. Jude experience with re-irradiation for recurrent ependymoma [5]. Thirty-eight patients with initially localized ependymoma at the time of definitive radiation therapy underwent a second course of radiation therapy at St. Jude Children's Research Hospital after local (n=21), metastatic (n=13) or combined (n=4) treatment failure. The re-irradiation method included radiosurgery (SRS, n=6), focal fractionated (FFRT, n=13) or craniospinal irradiation (CSI, n=19). SRS resulted in significant brainstem toxicity and one death using a median SRS dose of 18Gy. There was only one

long-term survivor. Focal fractionated re-irradiation was used in 13 patients who were followed for a median of 30 months. Three failed with metastatic disease and the 3-year event-free (EFS) and overall survival (OS) was 71% + 14% and 67% + 16%, respectively. There were no cases of necrosis with a median combined dose of 111.6Gy localized primarily to the brainstem and cerebellum. The outcome suggested a high-rate of local control for re-irradiation with limited adverse effects. CSI was administered to 12 patients with isolated metastatic failure after metastasectomy. The median combined dose at any point of overlap with prior irradiation was 99Gy. The 3 year EFS was 53% + 20% for patients with a median follow-up of 32 months. These data suggested that some patients with extensive recurrent disease may be salvaged with CSI, provided that surgery is a component of therapy. CSI was also administered to 4 patients with a history of combined local and metastatic failure: 3 of 4 patients subsequently failed demonstrating a potential limitation to this approach in patients who have more clinically aggressive disease. In summarizing this experience, it appears that SRS should have a limited role in the treatment of recurrent ependymoma and that patients with locally recurrent EP have durable local tumor control but remain at risk for metastasis. Salvage of isolated metastatic EP failures may be possible using CSI; however, those who have combined local and metastatic failure fare poorly despite aggressive surgery and re-irradiation.

To design this study we updated the experience at St. Jude Children's Research Hospital which included more than 47 children treated with fractionated re-irradiation after 2000. The 3 year EFS and OS rates were 49% + 8% and 70% + 8%, respectively. More and less favorable subgroups were identified considering initial pattern of failure, duration of initial disease control, neuropathology at initial recurrence, extent of resection at initial recurrence. The value of this approach is further supported by the lack of significant surgery-related complications and acceptable late effects of irradiation. We retrospectively reviewed 32 patients who underwent surgery prior to a second course of irradiation, 43% had no surgical complications and facial nerve weakness in 6 patients (21%) lead the list of identifiable complications including CSF leak/pseudomeningocele (7%), lower cranial nerve weakness (7%), cerebellar ataxia (7%), hemiparesis (7%), tracheostomy/gastrostomy (3%) and subdural effusion requiring shunt (3%). Late complications have not been systematically reviewed for these patients.

The St. Jude approach to re-irradiation has been partly validated by investigators at the University of Toronto. From their institutional experience including the years 1986 – 2010, they analyzed the outcomes from 47 patients with recurrent disease [5]. Twenty-nine patients were treated with various combinations of surgery and/or chemotherapy and 18 were treated with a second course of irradiation. Re-irradiation included ≥54Gy focal irradiation, with or without craniospinal irradiation and with or without surgery. Three-year OS was 7% ± 6% and 81% ± 12% for non-re-irradiated and re-irradiated patients ($P < 0.0001$). Time to second progression after re-irradiation was significantly longer than time to

first progression. There was improved progression-free survival (PFS) for tumors with evidence of DNA damage (n=15; p=0.002). Overall treatment effects appeared limited. A decline in intellectual function was observed in assessed patients.

The aggressive nature of salvage therapy using surgery and re-irradiation for relapsed ependymoma requires consideration of the clinical characteristics of the patients. Children with ependymoma tend to be young. Most are under the age of 4 years at the time of initial treatment. Children in this age range are vulnerable to the effects of radiation therapy and its use in frontline management has only recently been adopted. Historically, the pattern of failure for children with ependymoma treated with surgery and radiation therapy has been local. With improving rates of gross-total resection and high dose irradiation with doses ranging from 54-59.4Gy, the pattern of failure has become mixed with a higher proportion of patients failing with metastatic disease [6]; nevertheless, local failure as a component of failure remains high. The recent use of conformal radiation therapy has reduced the volume of normal tissue receiving the highest dose leaving open the possibility of re-irradiation in the setting of failure [7]. The potential young age of these patients at the time of failure should be considered among the indications for re-irradiation and suggestions with regard to dose and volume.

The indications for re-irradiation require exploration and dose and volume guidelines need to be established. The St. Jude experience defined three clinical risk groups that might help select patients for a particular treatment. Patients who progress at the primary site with no evidence of metastatic disease should be eligible for resection and re-irradiation using focal fractionated or craniospinal methods. Craniospinal irradiation might be considered for older patients based on the risk for metastatic progression. Focal fractionated irradiation should be the only option for younger patients to minimize the side effects of treatment. Patients with local failure should be offered both treatment options with recommendations dependent on patient age, prior treatment and morbidity and other factors balancing the potential for cure with the risk of long-term effects. The low negative predictive value of CSF cytology and neuraxis imaging affect the selection of treatment for this group of patients. Improving the negative predictive value of these tests may be considered in this study. Patients who progress with metastatic disease but who remain controlled at the primary site should be considered for metastasectomy and craniospinal irradiation. This group of patients may have disease burdens ranging from the resectable oligometastasis to extensive and unresectable neuraxis disease. Controlling metastatic disease requires a combination of craniospinal irradiation to neuraxis tolerance and supplemental irradiation to areas at highest risk for disease progression. Definitive treatment of these patients often requires exceeding generally acceptable normal tissue tolerance limits for brain and spinal cord. Patients who progress with combined local and metastatic failure, or diffuse neuraxis metastatic disease after prior radiation therapy appear to fare poorly with a second course of radiation

therapy although the number of patients with these clinical features appears to be small. Nevertheless, they should be considered for this treatment protocol that will set the stage for future experimental therapy including a combined modality approach that would involve craniospinal irradiation.

Patients who progress with local failure require careful neuraxis surveillance for metastatic disease and aggressive local resection with definitive evidence that the recurrence was indeed local. The nature and timing of the local failure may provide helpful clues about the risk of neuraxis dissemination and move caregivers to recommend focal or craniospinal treatment. The specter of metastatic disease may be reduced in a patient who experiences disease progression where residual tumor was known to remain after initial surgery or in a patient who develops obvious local failure relatively late > 3 years after radiation therapy. The clinical condition and age of a patient also require consideration, very young or debilitated patients may not fare well with craniospinal irradiation. Drawing a parallel to the frontline treatment for medulloblastoma, we do not propose a lower age cutoff for craniospinal irradiation but consider it to be a reasonable option in children over the age of 3 years since craniospinal irradiation is a treatment option for newly diagnosed and similarly aged children with medulloblastoma on frontline trials.

Exploring normal tissue tolerance with re-irradiation can lead to lethal complications or tremendous morbidity. This is readily apparent in patients treated with radiosurgery when the treatment volume included portions of the brainstem. Toxicity is always a concern for patients treated with fractionated re-irradiation regardless of the follow-up interval. While changes on imaging, and to a lesser extent with symptoms, may be apparent in some patient, most appear to avoid major effects. Those who do not have complications tend to be those with a negative history for prior treatment complications and a long interval between the first and second course of irradiation. There are several maneuvers to limit the side effects of treatment including the timely treatment of necrosis or potential necrosis. Our technique of re-irradiation using a combination of CSI and boost treatment seeks comprehensive coverage of the neuraxis. Shielding large volumes of previously irradiated tissue invites re-seeding. We have successfully limited side effects in patients with radiation necrosis and transient myelopathy using hyperbaric oxygen therapy. The time interval between courses of radiation is recognized along with other clinical factors, such as the specific region of the brain or spinal cord, as an important variable to consider when offering retreatment [8]. Although investigators have shown by experimentation or in clinical studies that the spinal cord may tolerate re-irradiation to relatively high-doses [9, 10], we have restricted retreatment to the spinal cord when administering craniospinal irradiation to patients who had prior infratentorial irradiation that involved the upper cervical spinal cord. The addition of craniospinal irradiation to a dose of 39.6Gy and to regions treated to less than 30% of the previously prescribed 54Gy achieves a biologic effective dose (BED) of approximately $96Gy_2$ whereas overlap of the entire cervical cord with the

combined doses of 54Gy and 39.6Gy would achieve a BED of approximately 246Gy_2. The former value falls within the lower range and the latter falls within the upper range of the previously reported cumulative spinal cord doses of 102-181.5Gy_2 where the risk of myelopathy was estimated at 25%. In our patients, categorized as intermediate risk based on the cumulative dose, the BED of the first course of treatment was about 129Gy_2 [9].

Re-irradiation for recurrent primary brain tumors has been a long-standing treatment option with investigators recognizing the attendant risks of necrosis or neurologic complication [1, 11]. One published series reported a 9% risk of necrosis and overall complication rate of 29% among 34 patients with primary brain tumors, including children, undergoing fractionated re-irradiation to a median combined dose of 79.7Gy (range 43.2-111Gy) [1]. This series showed only a modest palliative and survival benefit in a diverse group of patients. A more specific evaluation of combined re-irradiation and lomustine was conducted in a small cohort of patients with high-grade glioma demonstrating a median OS of 13.7 months. The re-irradiation dose was limited to 34.5Gy in 23 fractions with a median interval between first and second courses of irradiation of approximately 14 months [12]. With the advent of conformal radiation therapy investigators have attempted to minimize the dose to normal tissues when re-irradiation is attempted. One series included 20 patients with primary brain tumors unsuitable for brachytherapy or radiosurgery, predominantly high grade glioma. With a median re-irradiation dose of 36Gy (30.6-59.4Gy), and combined doses ranging from 80.6-119.4Gy, neurologic improvement and stabilization of disease was observed in more than 67% of patients [13]. Different dose and fractionated schemes have been attempted for similar patients. For example, low-dose (36Gy) fractionated re-irradiation has been applied successfully to predominantly adult patients with low and high-grade astrocytoma. The lack of observed toxicity might be attributable to the long interval between courses (median 50 months) for the low-grade patients and relatively short time to progression for the high-grade patients [14, 15]. Similar low, hypo-fractionated, doses have been applied in patients with high-grade glioma and ependymoma [16] with modest results. Focal fractionated re-irradiation and radiosurgery for medulloblastoma appears to be safe, provided the doses are relatively low, and locally effective; however, the overall results are poor in a tumor system prone to metastatic failure not unlike ependymoma [2].

To minimize the risks to the patient, there should be a 9-month interval between the start of the first course of radiation therapy and the start of the second course. The rational for this eligibility inclusion criteria including avoiding treatment of patients who have not passed the usual time period after the initial course of radiation therapy when necrosis might begin to appear and increasing the time interval between the start of the first course of radiation therapy and the second course, a known factor to precipitate necrosis. Brainstem radiation necrosis after the initial course of radiation therapy usually occurs within 6 months of completing radiation therapy or less than 8 months after the start of irradiation [6]. We would not want to initiate a second course of treatment for a patient that has

not passed this phase. Because the follow-up of children with ependymoma may vary between 3 and 4 months, it is reasonable to be conservative and specify an interval of 9 months. Further, patients who experience necrosis after a second course of irradiation appear to have a higher risk when the interval from first to second RT course is shorter than 6 months. This has been documented in two series [9, 17]. Fortunately, tumor progression during the first year after the initial course of radiation therapy is uncommon.

Patients treated with a second course of irradiation at St. Jude have not been systematically evaluated for late effects. Among the 23 patients who had not failed salvage therapy, we observed that 4 had notable disabilities. The remaining patients continue to be followed and the magnitude of side effects has been greatest among those treated with craniospinal irradiation. Given the very small volume that is targeted for focal fractionated re-irradiation, barring structure damage to the brainstem, the risks of endocrinopathy, hearing loss and cognitive decline do not appear to be significantly greater that that observed after the initial treatment course.

There are five domains of investigation which combine to support the primary and secondary objectives of this study. These include 1) the statistical design to estimate outcome (PFS and OS) which encompasses the evaluation of extent of disease, stratification, treatment and how disease progression is defined, 2) investigational imaging using MR imaging and PET, 3) clinical and neurological evaluation not limited to neuro-cognitive testing, ophthalmology and audiology, 4) biological studies and 5) functional outcomes including quality of life.

Three-year PFS and OS endpoints are appropriate for this protocol. The endpoint of PFS is based on data from our recent series suggesting that most newly diagnosed patients experience progression within the first 3 years after radiation therapy [6], regardless of whether progression is local or distant. Most of the patients enrolled on this study will have had their initial progression during this time interval. This will allow us to calculate of a ratio of time to second progression (PFS2) to time to initial progression (PFS1) [17]. The endpoint for OS is based on our unpublished experience which suggests that few patients live more than 24 months after recurrence when treated with chemotherapy alone.

Correlating clinical and biological factors with PFS and OS is aimed at learning more about the biology of ependymoma and risk factors for initial and second progression. By nature, patients treated on this study will be considered a high-risk group. Many will have had subtotal resection prior to the initial course of radiation therapy. It will be important to review the initial treatment for these patients and consider that some might have fared better after their initial course of irradiation, had surgery or radiation therapy been further optimized. For example, patients with initial subtotal resection who develop local progression and through this protocol achieve gross total resection will be considered amongst those who were not optimized surgically prior to their initial course of irradiation. Patients

initially treated with doses lower than 50Gy, especially in the setting or residual disease would also fit this category. These patients will be ineligible for this protocol. Other factors such as targeting for the initial treatment and subsequent pattern of local-regional failure will be considered.

Tissue acquisition (initial and recurrent) will enable a number of unique opportunities. Patients with local progression treated with surgery prior to their second course of irradiation will have their tissue acquired for biology study. These patients will be considered to have less radiosensitive and more aggressive tumors. The pattern of failure for these patients after second irradiation will provide unique insight into their inherent radioinsensitivity (local failure) or metastatic potential (neuraxis failure). Another unique opportunity will be to study metastasectomy specimens. These tissues will likely represent metastatic tumor that has not been exposed to irradiation and may be considered virulent by nature of its metastatic potential unless iatrogenic.

There is significant variability of extent of disease at the time of initial treatment failure. One of the primary concerns among caregivers is morbidity. The toxicity of this regimen requires careful evaluation with attention to the early and late effects of treatment. While the attribution of toxicity to prior treatments, surgery performed as a part of this study, and radiation therapy dose and volume is of academic importance, it is more important to consider the toxicity of the combined regimen to determine the overall value of this approach. Indeed, some consider metastasectomy to be an extreme maneuver; however, in our experience, the morbidity of resection of locally recurrent tumor, which is more widely accepted, may be greater than that for metastasectomy. Sites at which tumor resection is not feasible will be monitored for therapy response and used to fulfill secondary imaging objectives. In monitoring response to therapy, sites will be classified based on prior treatment with metastatic sites providing a unique opportunity to quantitatively monitor response to irradiation in a treatment-naïve setting.

Composite radiation planning data is critical to the evaluation of these patients. The tolerance of the nervous system to high-dose irradiation is remarkable. The underlying effects of high-dose irradiation on structure and function will be studied. We support the hypothesis that normal tissue tolerance is dependent on both radiation dose and volume, that the tolerance of any volume to high-dose irradiation is dependent on the proportional volume of the entire organ exposed to radiation dose, the so called dose “bath and shower” effect. To study this more thoroughly, we have acquired hardware and software to accept the treatment planning data from most commercial systems so that patients initially irradiated at other centers will have their volumetric dose data combined with those of this study for a more accurate representation of volumetric dose to normal tissue. This is an important maneuver since registration of follow-up imaging with composite dose-volume data will be requisite to monitoring response to therapy and evaluating structural and functional changes.

We need to determine clinically significant side effects in the context of prior treatment, prior treatment complications, pattern of failure and disease burden, and radiation dose integrated over the central nervous system and specific functional subunits. Considering clinical factors that predict morbidity, there are critical combinations of tumor, surgery and radiotherapy effects that will lead to clinically significant morbidity after a second course of irradiation. There are critical events leading to initial diagnosis, critical events in the peri-operative period and critical radiation dose and irradiated volume tolerance levels that will predict for side effects after a second course of irradiation. A detailed medical history with supportive clinical data is required for safe second irradiation and exposes clinical factors that predict for morbidity. Our greatest concern is for patients with infratentorial tumor location and necrosis of the brainstem, cerebellum, spinal cord or other central intra-axial structures. History and supportive documentation may include but should not be limited to the following: presenting signs and symptoms and their duration; tumor imaging features at presentation: size, location, displacement and invasion of normal structures; hydrocephalus: extent, treatment and complications including temporary or permanent ventriculostomy and subsequent complications, infections, revisions and ventricle response; peri-operative factors: extent and number of surgeries, surgical complications including infections, transfusions and anesthesia records detailing brainstem neurological and vital functions including heart and respiratory rate and rhythm, blood pressure and required management and medications; post-operative neurological function, imaging findings and clinical course of recovery. Similar detailed information is required at the time of recurrence including patient demographic data, serial imaging and clinical evaluations, documented radiotherapy history including electronic record of dosimetry (radiation dose and volume, normal tissue and target volumes, dose heterogeneity), history of chemotherapy, and time course of functional deficits affecting neurological (neurological examinations, hearing and vision testing), endocrine (deficits and replacements) and cognitive systems (fundamental psychology and developmental data). These data will help us to assess the morbidity of surgery after prior irradiation.

2.2 Neurological, Endocrine and Cognitive Studies

Neurological, endocrine and cognitive effects of irradiation are the most common focus of concern for caregivers. Neurological effects most often include cranial nerve, motor and cerebellar dysfunction. The effects of surgery and irradiation on neurological function have been previously described for children with ependymoma initially treated with aggressive surgery and irradiation [18]. There is little doubt that patients who experience tumor recurrence and undergo additional surgery and radiation therapy will experience or be susceptible to treatment effects. These have not been formally documented. Such documentation will be the goal for this study both to describe the morbidity of the condition as well as to identify clinical covariates that impact other measures of CNS effects. Neurological deficits include transient and permanent damage to hearing and

vision and loss of neurological function associated with surgery, radiation therapy and in the extreme – necrosis of brain or spinal cord.

The endocrine effects of retreatment may compound the existing risk for any endocrinopathy which ranges up to 25% among patients successfully or unsuccessfully treated with initial surgery and irradiation [7]. Because most recurrences after initial treatment occur about 18-26 months after treatment, patients enrolled on this study may have ongoing endocrine deficiencies that need to be addressed and document to assess the toxicity of the proposed treatment regimen. Children will undergo endocrine evaluation and provocative assessment of growth hormone and adrenal axis hormones.

2.3 Psychology Studies and Neurocognitive Outcomes

Children who receive radiation therapy for ependymoma are at increased risk for impairments in cognitive functioning [19]. There is strong evidence to suggest that total radiation dose and volume of irradiated brain play a significant role in cognitive outcomes, with lower doses of cranial radiation associated with less intellectual impairment [20, 21]. Given this finding, it is predicted that re-irradiation may be associated with additional cognitive morbidity; thus, it is imperative that cognitive outcomes be closely monitored. Cognitive monitoring conducted within the context of this protocol could significantly impact determinations regarding the acceptability of this treatment approach.

A progressive decline in intellectual functioning (IQ) after radiation therapy for childhood brain tumors has been well-established [22-25]. Increased utilization of special education services has also been reported and cranial irradiation has been associated with poor academic performance on standardized measures in childhood brain tumor survivors [21, 23, 26, 27]. Further, studies have found declines in academic functioning for children 2 to 5 years after irradiation [28, 29]. Previously reported findings from the RT-1 protocol indicate that reading, in particular, may be more vulnerable than other academic skills and may decline despite stable intellectual functioning in children treated for ependymoma with conformal radiation therapy [30].

More recently, research investigators have tried to identify specific cognitive deficits that may underlie global declines in intellectual function or academic achievement. Reports of deficits in attention [31], working memory (online maintenance and manipulation of information) [32], and processing efficiency [33] are most prevalent. These emerging areas of core deficit are informative as nearly half of age-related improvements in IQ can be accounted for by developmental improvements in working memory and processing speed [34]. Accordingly, these cognitive domains will be the focus of serial monitoring.

Radiation therapy is a well-established cause of changes in cerebral white matter [35]. There is accumulating evidence to suggest that reduced cerebral white matter accounts for a significant proportion of the observed decline in IQ among

survivors of childhood brain tumors. For example, in a longitudinal study examining the impact of two craniospinal irradiation doses (conventional [36Gy] and reduced [23.4Gy]) in the treatment of medulloblastoma, Reddick and colleagues found a significant decrease in cerebral white matter volumes, in contrast to expected developmental maturation [36]. Further, the rate of white matter decrease was more rapid in patients who received the higher radiation dose. Reddick and colleagues have also demonstrated that a primary implication of reduced cerebral white matter volumes in children treated for brain tumors is compromised attention abilities that lead to a decline in IQ and academic achievement [37].

Risk factors most consistently associated with cognitive problems following treatment for childhood brain tumors include not only treatment intensity (i.e., radiation dose/volume) but also younger age at treatment [38], longer time since treatment [39], female gender [40] and complicating medical factors [41]. Findings from children treated for ependymoma on the RT-1 protocol revealed that tumor location, number of surgical resections, longer symptomatic interval, pre-irradiation chemotherapy, pre-existing endocrine deficiencies, hydrocephalus and younger age at treatment were associated with greater cognitive problems [30, 42]. Accordingly, relevant demographic and clinical factors will be included in models investigating the effect of re-irradiation on cognitive outcomes.

2.4 Sleep Disorders, Fatigue and Quality of Life

Survivors of ependymoma retreatment are known to have neuroendocrine deficiencies, visual deficits, seizure disorders and hypothalamic obesity due to the number of surgery procedures, dose and volume of radiation therapy and tumor location. Damage caused by repeated and aggressive surgeries and radiation also results in sleep disturbances, daytime hypersomnolence, defective-short-term memory, limited concentration span, and other symptoms. Reports of sleep disturbances and long term outcomes in pediatric ependymoma patients are limited; however, adult patients with ependymoma report moderate to severe symptoms including fatigue and sleep disturbance [43].

The literature is limited regarding sleep disturbance and symptoms among pediatric patients re-irradiated for recurrent brain tumors. A recently published review of patients with recurrent medulloblastoma described toxicities and noted an increased risk of necrosis among patients re-irradiated compared to nonirradiated [44]. The brain tumor retreatment was suggestive of prolonged survival, with the benefit best for those initially treated as standard risk. However, the literature is limited in describing patient reported outcomes of symptomatology.

This study provides an opportunity to investigate the potential relationships between characteristics of sleep quality and daytime sleepiness/fatigue, quality of life, and treatment symptoms within a large cohort of extensively treated brain tumor survivors. Clinical experience suggests that a variety of clinical sleep

disorders may be present in this patient group including insomnia, obstructive sleep apnea, daytime sleepiness, circadian rhythm dysfunction and/or fatigue. Sleep has a restorative function for healthy and ill children and adolescents as it provides a period of increased protein synthesis, cellular division, and growth hormone release that contributes to tissue renewal [45, 46] and compensates for energy deficits acquired during daily functions [47, 48]. Sleep patterns reflect neurological maturation, but stability in those patterns in terms of total night sleep and night awakenings occurs by age 4 or 5 years [47, 48]. A gradual reduction in nocturnal movement intensity occurs in children and adolescents [49, 50] with minimal differences being found between children who are 3 – 5 years of age, 8 – 12 years or young adults who are 18 – 24 years of age [51]. When self-report methods are used in sleep studies, significant gender differences are noted in sleep quality with females reporting significantly lower sleep efficiency than do males [52]. Weight has also been associated with sleep quality. Overweight children and adolescents have documented shorter sleep time, later sleep onset and more disturbed sleep than healthy controls [53]. Academic grades are adversely affected by short or poor sleep [54, 55]. Finally, children with a confirmed diagnosis of depression were also found to have poorer sleep quality [56]. Given these important child or adolescent characteristics associated with sleep, we will collect information on patient age, gender, weight (BMI), and other clinical factors at diagnosis and will examine the association of each with sleep, daytime activity and fatigue outcomes.

Modulation of sleep/wake patterns and sleep architecture is orchestrated by specific neuronal populations and pathways that involve the brainstem, diencephalon, and thalamus [52, 57, 58]. In healthy individuals, neuroanatomical and neurophysiological systems provide the substrate for well-organized and predictable sleep/wake cycles. Restorative sleep is typically experienced during the night and sustained wakefulness across the day. Wakefulness is promoted by several systems that include the reticular formation (RF) of the brainstem (ventral medullary, central pontine, and midbrain reticular formation), the posterior hypothalamus, and the basal forebrain [52, 59]. Neurophysiological expression of wakefulness is characterized by desynchronication of cortical activity. From a neurochemical perspective, catecholamine- and acetylcholine-containing neurons modulate the activity of subcortical and cortical neurons during wakefulness. Histamine, hypocretin [60], and a variety of other neuropeptides elaborated by the posterior hypothalamus enhance wakefulness. Circulating blood-borne neurochemicals such as epinephrine, histamine, and glucocorticoids can also serve to enhance wakefulness. Another neurochemical, melatonin is produced by the pineal gland and is important in the hypothalamic and pituitary regulatory functions. Melatonin secretion occurs at night and insufficient secretion has been associated with disorders in delay of sleep, with an influence on circadian rhythm [61].

Non-rapid eye movement (NREM) sleep is characterized by synchronized neuronal activity that is modulated by several integrated neuronal systems.

Neurons involved in NREM sleep are located in the solitary tract of the medulla, raphe nuclei of the brain stem, reticular thalamic nuclei, anterior hypothalamus, preoptic area, basal forebrain, and the orbitofrontal cortex [52, 57, 62]. Thalamo-cortical projections and networks support the synchronized cortical activity that comprises NREM sleep [63, 64]. This neuronal network is GABAergic in character. Serotonin-containing neurons of the brain stem raphe serve to dampen sensory input and inhibit motor activity, which promotes the emergence of deep NREM (slow wave) sleep. Adenosine neurons are located in the hypothalamus, promote NREM sleep, and are blocked by caffeine and xanthines. GABA, opiates, somatostatin, and alpha-melanocyte-stimulating hormone facilitate NREM sleep. Benzodiazepines bind with GABA receptors to enhance NREM sleep. CSF-borne factors such as opiate peptides (beta-endorphin, enkephalin, and dynorphin) play roles in sensory modulation and analgesia and these processes are related to sleep onset and maintenance. Several blood-borne factors also promote NREM sleep including muramyl peptides from intestinal gut bacteria (stimulating production of interleukin-1 and other cytokines), cholecystokinin, and insulin [52].

Rapid eye movement (REM) sleep alternates with NREM sleep in a predictable and periodic fashion across the major sleep period. REM sleep is supported primarily by neuronal populations in the dorsolateral pons and caudal midbrain [65]. During REM sleep muscle atonia occurs as a normal and expected phenomenon [66, 67]. This process is mediated by neurons in the midbrain perilocusceruleus region with connections to the medullary reticular nucleus via the tegmentoreticular tract. In addition to muscle atonia, a variety of other REM related phenomena occur under normal circumstances including dream mentation and imagery, rapid eye movements, fluctuations in heart rate, respiratory rate and depth, hippocampal theta [68] activity, and relative loss of thermoregulatory ability. The precise function of REM sleep is not fully understood.

The sleep architecture of NREM and REM periods alternate throughout each night of sleep in cycles of 90 to 110 minutes for children, adolescents and young adults. The three stages of NREM together take approximately 36 to 75 minutes and REM approximately 5 minutes [69, 70]. Sleep experts generally suggest a 90-minute sleep cycle for children and adolescents [71].

Given the critical importance of the neuroanatomical, neurophysiological, and neurochemical systems for modulation of sleep/wake states, it is apparent that anatomic lesions in key locations of the brainstem, diencephalon, and thalamus may lead to functional disruption of sleep and/or wakefulness. Loss of wakefulness can occur with lesions in the pontine and midbrain tegmentum, in the glutamatergic neurons of the reticular formation, in the noradrenergic locus coeruleus neurons, in the posterior hypothalamus (histaminergic or hypocretinergic neurons), or in the cholinergic basal forebrain neurons. Loss of natural sleep can occur in association with lesions of the lower brainstem or preoptic area in the forebrain [72].

The literature regarding cerebral neoplasms and sleep is limited by the small number of reports, small sample sizes, and the observational and retrospective nature of the studies. Few reports involve children. Several reports provide information about the "hypersomnolence syndrome" that occurs after cranial radiation treatment [73, 74] and several others describe the association of brain lesions and cataplexy [75], and brain lesions and obstructive or central sleep apnea [76-78]. One study provides polysomnographic (sleep study) data from patients who were studied before and after surgery [79]. In a retrospective report by Rosen et al, 14 children with CNS tumors are characterized regarding the range of sleep problems and disorders that are present following surgical resection, cranial radiation, and in some cases, chemotherapy [80]. This proposal would be the largest study describing the trajectory of sleep complaints and disturbances among a cohort of patients with recurrent ependymoma.

A recent study evaluated adult survivors of brain and spine ependymoma assessing the impact of symptoms on their daily life [43]. The patients reported the most severe symptoms to include fatigue (44%), numbness/tingling (39%), pain (36%), and disturbed sleep (34%). The specific sleep disturbance among patients with ependymoma was not examined nor the specific sleep symptoms. This proposal will assess for prevalence of fatigue and sleep disruption and associated symptomatology. We will assess for excessive complaints of daytime sleepiness that may be secondary to obstructive sleep apnea or may indicate secondary narcolepsy due to the medical condition. Excessive sleep complaints will be measured with the Symptom Distress Scale and Epworth Sleepiness. Quality of Life will be measured with the Peds QL Brain Tumor. Fatigue will be measured with the Peds Multidimensional Fatigue Scale.

Sleep efficiency, latency, and total sleep time will be assessed with actigraphy. The actigraph has been used in monitoring sleep in children and adolescents because it is a low cost, non-intrusive yet keenly sensitive measurement approach. Actigraphy has been used to validate parental reports of their child's sleep abnormalities [81] while producing more objective and accurate data as compared to parental reports [82, 83]. Functionally, the actigraph detects and records movement. Movement triggering the actigraph is relatively high during wakefulness and decreases to near-zero values during sleep. Analysis of actigraphic records reveals sleep-wake patterns that correlate closely with patterns obtained via polysomnographic recordings and behavioral observations [81, 84, 85]. Sleep-wake scoring algorithms from actigraphic data from the dominant and nondominant hands of 16 adolescents were determined to be essentially the same; similarly, the overall agreement rates from actigraphic data from both hands with polysomnography scoring during one laboratory night was between 91 and 93% [82, 86]. Actigraphy has been used to document the efficacy of behavioral interventions designed to correct sleep disturbances in well infants and toddlers [81, 86] and to document the hyperactive state and response to therapy in children with attention-deficit hyperactivity disorder [87, 88]. In summary, actigraphy is

able to sensitively capture change in sleep-wake patterns before and after behavioral or medical interventions, and actigraphic data from either wrist is highly similar.

We will assess sleep quality with actigraphy at baseline and yearly over a 5 day assessment period with measurement of the following.

Actigraph Terms

Duration	Minutes from start to end of interval
Activity Mean	Mean activity score (counts/epoch)
Activity Median	Median activity score (counts/epoch)
Activity SD	SD of Activity mean
Wake Minutes	Total minutes scored as Wake
Sleep Minutes	Total minutes scored as Sleep (Sleep + Light Sleep)
% Sleep	Percent minutes scored Sleep (100*(Sleep + Light Sleep)/Duration)
Light Sleep	Total minutes scored Light Sleep (Sadeh Infant Algorithm)
Sleep Efficiency	(100 * Sleep Minutes/(O-O duration))
Sleep Latency	Minutes to start of first 20 minute block with > 19 minutes sleep
Wake After Sleep Onset (WASO)	Wake minutes during O-O interval
Acceleration Index	% epochs with > 0 activity score
Bad Epochs	Total bad epochs
Wake Episodes (WE)	Number of blocks of contiguous wake epochs
Mean Wake Episode	Mean duration of WE (minutes)
Long Wake Episodes	WE >= value in Options: Sleep: Sleep Statistics Criteria text box
Longest WE	Duration of longest WE (minutes)
Sleep Episodes (SE)	Number of blocks of contiguous sleep epochs
Mean Sleep Episode	Mean duration of SE (minutes)
Long Sleep Episode	SE >= value in Options: Sleep: Sleep Statistics Criteria text box
Longest SE	Duration of longest SE (minutes)

Acceleration Index—the acceleration index (AI) is calculated by the formula:

AI=2p-1

Where p is the proportion of the interval required for 50% of the total activity in the interval to be completed. For example, for a 1-hour interval, if the activity total for the interval was 1000 and 800 counts occurred in the first 20 minutes of the interval, p would be 20/60 or 0.33. Doubling p and subtracting 1 scale the index form -1 to +1. Thus, negative values represent slowing during the interval, 0 represents uniform distribution of activity during the interval, and positive values represent acceleration during the interval.

Epoch—this is the time interval used for activity sampling. It is usually set to 60 seconds, though for some actigraphs, it is programmable from one second to many minutes. The epoch duration determines the maximum temporal resolution of the activity data. For sleep estimation, the epoch duration must be 60 seconds, or an integer factor of 60 seconds. Down intervals—represent the major sleep period of the day, when subjects are in bed and trying to sleep. These intervals are sometimes called "In-Bed" intervals. Up intervals—represent the times between successive Down intervals. Thus there will always be one fewer Up Interval than Down Intervals. O-O intervals—are sub-intervals of the Down Intervals that estimate the true sleep period. It represents the time from sleep Onset (as defined by the sleep latency) to sleep Offset (the end of the last sleep episode in the Down Interval). Thus an O-O interval represents the Down Interval minus the sleep latency and any terminal wake in the down interval.

Each patient will be provided with a postage paid return mailer for actigraphy return. Once the actigraphy has been returned to the Division of Nursing Research, each participant will receive a $25 gift card to reimburse for the time and any inconvenience experienced as a result of taking part in the sleep study.

2.5 Physical Performance and Movement

Physical function is goal directed. Movement takes place within the environment as a mechanism for survival, adaptation, learning, and interaction [89]. When individuals are limited in their abilities to move, they are less likely to be able to meet every day needs. For example, someone who cannot reach overhead may not be able to get a glass or plate out of the cupboard to set the table. A person with weak legs may not be able to get up and down from the floor or in and out of the bathtub and a person with poor cardiopulmonary fitness may not be able to walk up and down the aisles of a grocery store, or up and down the stairs in front of a church. Movement is an essential part of everyday life. Mobility limitations interfere with participation in roles at home, work and in the environment [90].

During infancy and childhood, both the size of the body and the maturity of the body systems define and limit physical performance abilities. Early development is survival oriented and includes lifting and turning the head, coordinating sucking, swallowing, and breathing, crying to indicate needs, and making facial expressions to interact with the caregiver. As children grow and gain control of movement, they begin to explore their environments and gain initial independence with everyday physical tasks, like eating, dressing and playing. Throughout childhood and adolescence, the body continues to grow and mature until all systems are optimized, designed to operate at peak efficiency. Movement practice allows refinement of motor skills so that participation in recreational physical activities like track, swimming, baseball, basketball, ballet and gymnastics is possible [89, 91, 92].

In typically developing children, societal roles, lifestyle changes and eventually aging impact the development and maintenance of optimal physical function [93]. Decreased exposure to physical activity because of time spent indoors, watching television, or in front of the computer, accompanied by poor dietary choices may result in overweight or obesity and make movement difficult and undesirable [94]. Cardiopulmonary fitness and muscle strength may not be fully optimized, resulting in poor endurance and weakness [95]. Progression into adulthood with less than optimal physical function can be problematic, as both a habitual sedentary lifestyle, and the requirements of work specialization, for example, sitting at a desk, may perpetuate and contribute to declining physical efficiencies over time [96].

Function, physical performance and participation in everyday tasks

Function is an umbrella term that considers health and health related status as an interaction of a person with society. Physical performance is one component of function, and when limited, may contribute to disability. Normal function includes the ability to perform movement related tasks required for everyday activities. Typical physical performance progresses from infancy to toddlerhood as head lifting, rolling, crawling, sitting, pulling to stand, and walking. Toddlers learn to run, jump, hop and skip, so that by age 5 or 6, they can participate in vigorous play activities and organized physical recreation. Motor skills are refined throughout childhood and movement force is optimized in adolescence. Young adults typically have all of the skills and capacity necessary for participation in everyday tasks including activities that require extreme movement coordination, like bathing and dressing, and activities that require a fair amount of physical capacity like running and participation in sport. Refined skill and capacity vary across the normal population; not everyone has the capacity to climb Mount Everest. However, most people can bath, dress, get out of a chair, walk several blocks, climb stairs and perform the physical tasks required for them to maintain their households or do their jobs.

Physical performance is dependent on the structural integrity and physiologic function of the nervous, musculoskeletal and cardiopulmonary systems, to provide a foundation upon which normal movement for everyday tasks can be accomplished. Movement created by the coordination of these three systems is also dependent on the health of the other body systems; that is, on intact skin to protect the body, on the gastrointestinal and urinary systems to process nutrients and body waste, and on the endocrine system to regulate metabolism. The general composition of the body is extremely important to movement as it governs the strength of the skeleton upon which movement occurs, the amount of lean muscle available to produce force, and the amount of body fat that must be carried while performing daily tasks. The structure and functions of the systems that govern movement are typically measured by assessing flexibility, balance, coordination, power, and cardiopulmonary fitness [89]. Lack of capacity can be defined for these measures. Impaired capacity in these systems is typically associated with overall physical performance limitations.

1. Flexibility is the capacity to bend and is based on the pliability of the muscles, connective tissue and skin, and on the ability of a joint to move through its range of motion. Girls are typically more flexible than boys [89, 92, 97].
2. Balance is the ability to maintain center of gravity over a base of support, thereby maintaining an upright posture either at rest or during movement [98]. Balance improves throughout childhood, is better in girls than boys during childhood, and plateaus in adolescence where young men's skill surpasses that of young women [99].
3. Coordination implies that the nervous and musculoskeletal system work together to produce smooth, efficient movement. It implies that the muscles work at the right time with the right intensity [100] to produce movement. Coordination is needed to get button or zip clothing, run, skip, and drive a car.
4. Power is the rate at which work is done and includes both muscle strength and speed of movement. It requires a muscle to develop tension and produce the force to move a body part through range of motion. Power increases during childhood and peaks during adolescence and young adulthood [101].
5. Cardiopulmonary fitness is the ability of the cardiac and pulmonary systems to provide muscles with an adequate supply of oxygen for work. Capacity increases across childhood with age and peaks during young adulthood. Exercise capacity is typically quantified as maximal oxygen uptake (Vo_2max) and is a product of maximal cardiac output (liters of blood per minute) and arterial-venous oxygen difference (milliliters of oxygen per liters of blood). Fitness levels across populations vary primarily from differences in maximal cardiac output. Therefore, this measure closely corresponds to the functional capacity of the heart [102-107].

Physical performance in children treated for recurrent ependymoma

While early research has documented the impact of changing treatment on survival [17, 108] and some late cognitive late effects [30], little work has been

done to either specifically and objectively evaluate and describe physical performance, or to look at the impact of improved surgical and radiotherapy management techniques on physical disability in this population. A longitudinal assessment of physical performance and of movement related impairments among children undergoing retreatment for ependymoma, either with focal retreatment or craniospinal irradiation after additional surgery is important as it will provide insight into the specific nature and timing of physical disability in this population. It will help assess the effectiveness of this therapy, balancing disease control against functional outcomes, including movement related morbidity in long term survivors, and provide information for targeted rehabilitation interventions designed to restore physical function, teach compensatory strategies that overcome functional loss, or adapt the environment so survivors with persistent disability can participate optimally in life roles.

Childhood cancer survivors treated for brain tumors with radiation report increased rates of physical disability when compared to their siblings [109, 110], and demonstrate limitations in mobility, strength, flexibility, and cardiopulmonary fitness when evaluated with objective physical performance measures [111]. Long term physical disability is problematic. It interferes with play and family interaction in the young child, with school attendance and social participation in the school aged child, with normal adolescent activities and school participation in older children, and with normal social and work roles in young adults. Childhood cancer survivors with physical disability report reduced quality of life and are less likely to attend college, gain employment or get married than are their siblings [112, 113]. Unfortunately, in some cases of recurrent brain tumor, including ependymoma, the cost of curative therapy has been permanent physical disability, as radiation induced necrosis destroys a portion of the nervous system necessary to achieve normal movement [17, 114, 115].

Evaluation of the potential positive impact of new modalities and mechanisms to treat recurrent tumor on physical performance outcomes is important. Positive clinical outcomes provide evidence to support the use of emerging and state of the art technology, and identification of both positive and negative predictors of long-term outcome provide foundational information for future development of rehabilitation type intervention trials in those children and adolescents who might most benefit from an early plan to maintain their ability, mobility and long-term physical abilities. Mechanisms to optimize physical performance after surviving recurrent ependymoma, developed in response to the information gained when evaluating this clinical outcome, can be designed to allow these young survivors to become productive members of their communities and society.

From a global perspective, little information is available about physical performance outcomes among children treated for brain tumors, and almost no information specifically characterizes these outcomes among children who are treated with re-irradiation for recurrent ependymoma. In studies designed to measure short or long-term clinical outcome, these patients are usually a small

subset among a larger group of children with brain tumors, and are often evaluated only in a cross sectional, or one time point assessment. Very rarely, objective, person level function is measured. Most data comes from self- or proxy report questionnaires or from general clinician generated global scales of function. Nevertheless, there is some information in the literature describing overall brain tumor survivor outcomes that indicates that physical disability prevalence rates are potentially elevated in this population. Gains from the investigation proposed here will add to this literature. Knowledge of expected long-term clinical outcome may inform parents and clinicians during the treatment process, so they know what to expect and when and if to seek restorative rehabilitation services. This work will identify specific person and treatment related characteristics that predict poor outcomes, and potential physical impairments in this population that may be amenable to a rehabilitation type intervention.

Two reports from the Childhood Cancer Survivor Study enumerate self or proxy reported physical performance and functional outcomes in adult survivors of childhood brain tumors, and provide some indication of the impact of large radiation doses on long-term physical disability. The first report, published in 2005, indicated that physical performance limitations are prevalent among 26.6% of childhood brain tumor survivors, a rate 2.5 times higher than among siblings. In this cohort, treatment with radiation was associated with a 70% increased chance of reporting poor physical performance when compared to treatment with surgery alone [110]. In a subsequent manuscript from the same cohort, Armstrong et al. [109] completed a cross sectional analysis of long-term outcomes among adult survivors of central nervous system malignancies. This manuscript included 148 survivors of ependymoma. Both chronic medical conditions (82%) and functional loss were prevalent in this large cohort. Brain tumor survivors were 19.5 times more likely than siblings to report functional impairment, and 36.2 times more likely than siblings to report activity limitations. Weakness, sensory loss, pain, problems with balance and paralysis were common, and continued to develop, even at time points beyond 5 years off treatment. Higher doses of cranial radiation, particularly doses >50Gy, were associated with lower educational attainment, unemployment, never being married, and incomes of less than $20,000 per year. The brain tumor survivors characterized in these two manuscripts were treated between 1970 and 1986, prior to the advent of more contemporary imaging and radiotherapy techniques.

However, these data are supported by an investigation of measured physical performance outcomes in a more contemporary cohort of brain tumor survivors treated at the University of Minnesota or at St. Jude Children's Research Hospital [111]. Participants (n=78) and age, gender, and zip code matched controls (n=78) were compared on measures of muscle strength, mobility and cardiopulmonary fitness. Among brain tumor survivors who were, on average, 22 years of age, estimates of grip strength, knee extension strength and peak oxygen uptake were similar to expected values of individuals in their seventh decade of life. Radiation

to the posterior fossa or occipital/parietal lobes was associated with poor outcomes. Poor physical performance was associated with not living independently and with not attending college.

Only a few authors have specifically included survivors of ependymoma in investigations, and have usually document physical ability simply as one component of global clinical outcome [116]. At least one investigation has been longitudinal, but did not include children with recurrent disease [18]. Benesch et al [116] included 6 children with ependymoma when they developed the LESS scoring system for clinicians to use when quantifying late effects in children after radiation and chemotherapy for brain tumor. Neurological, endocrine, visual/auditory and an "other" category are included on this severity rating scale. Children with higher scores on this rating scale had lower quality of life scores than did those with lower scores, indicating an association between neurological outcome and overall quality of life. Morris et al [18] evaluated neurological morbidity in 96 children with ependymoma within 3 months of conformal cranial irradiation and every 6-12 months thereafter until 120 months post radiation. Assessments were performed by a neurologist and included a four point grading of multiple neurologic outcomes including muscle strength and strength, motor control, coordination and gait. Neurologic impairments were most prevalent at baseline and decreased over time. However, at 60 months post treatment, participants still had an average of 2.2 neurological deficits. There were 17 patients with at least one severely compromised function 60 months post therapy.

We could identify only one study among children with recurrent ependymoma who treated with re-irradiation that very briefly described performance type outcomes. Liu et al, [108] in a study designed to evaluate the curative impact of hypofractionated re-irradiation in 6 children with local recurrence of ependymoma, reported that 3 children had imaging changes consistent with necrosis 7-8 months after treatment. Among these 3 children, 1 had no physical symptoms, 1 had ataxia that resolved, and 1 had headache related pain treated with over the counter medication.

The literature describing function among survivors of childhood ependymoma is limited not only because of few papers and lack of longitudinal data, but also because functional outcomes are generally good after frontline therapy. The determination of disability has generally depended on clinician report rather than on measured values or on patient reported outcome. These issues make it difficult to determine either the real prevalence of physical disability, or the specific impairments that survivors have that contribute to their physical disability. Demographic and clinical characteristics have been reported to be associated with poor overall global function. However, because investigations have not specifically measured physical performance, risk factors for these specific outcomes are unknown. Information about the extent and nature of physical performance limitations, and about the risk factors for poor outcomes, is important for determining the need for resources and the type of resources that

might be needed to optimize functional outcomes. Knowledge about the timing of and the specific risk factors for poor outcomes may help identify those patients in particular need of interventions designed to prevent long term functional loss.

2.6 Neuroimaging

Patterns of recurrence of ependymoma have been little studied in the literature, but may provide valuable information regarding efficacy of initial radiotherapeutic target volumes. It would be expected that, given the history of prior focal RT, the pattern of recurrent disease would differ from that typically seen at initial presentation. Initial, pre-treatment conventional imaging and post-recurrence conventional MR imaging will be analyzed for spatial distribution of disease, compared to each other and compared to initial radiation dosimetry maps to evaluate how the disease pattern is altered in the post-irradiation brain.

Evidence of tissue damage, including atrophy and encephalomalacia, has been observed in untreated brain in initially successfully treated patients who, though initially without clinical evidence of function loss, subsequently experienced complications. By assessing alterations in structural, microstructural and physiologic properties of both treated and untreated brain tissue over time and comparing to dose distribution and measures of cognition and function over time, imaging-based biomarkers predictive of treatment-related functional or cognitive compromise may be established. Evaluation of response of primary site and metastatic disease to radiation therapy will be assessed using quantitative MR imaging and PET.

2.6.1 Magnetization-Transfer Imaging

As early damage to brain tissue can appear deceptively normal on conventional anatomic MR images [117], reliance on visual inspection may be insufficient to appreciate the true extent of microstructural damage. Diffusion tensor imaging has proved effective in delineating white matter tracts, and has demonstrated changes in fractional anisotropy (FA) and other diffusion parameters in normal-appearing white matter following radiation therapy above a certain threshold dose [118]. These changes in water diffusivity have been shown to correlate with damage to structural components of the white matter tracts [119].

Magnetization-transfer (MT) MR techniques offer an alternative approach toward evaluation of brain tissue integrity, via evaluation of macromolecular content. In this technique, the protons of MR-invisible macromolecules are saturated by manipulation of the radiofrequency (RF) pulse [120]. These protons then exchange their saturation by various mechanisms with the water peak. This results in a decrease in the detectable water signal, serving as an indirect marker of the size of the macromolecular “pool”. Because in white matter this pool is presumed to be largely due to myelin, changes in the magnetization-transfer ratio (MTR, 1-

Ssat/So) are felt to be representative in changes in myelination. Indeed, changes in magnetization-transfer ratio have been shown to correlate to white matter damage and recovery in multiple sclerosis and other white matter disorders [121, 122]. Changes in MTR in normal-appearing white matter (NAWM) have been found to precede the development of lesions in multiple sclerosis (MS); changes in MTR in normal-appearing gray matter [123] may have an even stronger correlation with clinical course [124, 125]. There is a strong possibility that, as in MS, invisible gray matter alterations may be a more sensitive predictor of clinical course following radiation injury. Though MT imaging has the potential to detect these changes in both gray matter and white matter prior to manifestation on standard MR sequences, there is a dearth of studies of MT in this setting, likely due to the historically long image acquisition time (~12 minutes for MT sensitized and non-MT sensitized sequences) limiting routine utilization [117]. However, this limitation has been overcome by the recent development of bSSFP –based MT techniques requiring on the order of 3.5 minutes total acquisition time, quite feasible for inclusion in a routine imaging protocol [120, 126].

Magnetization-transfer imaging with bSSFP technique in this protocol will serve three purposes: 1) comparison to DTI regarding sensitivity for radiation-induced white matter changes, 2) assessment of early cortical gray matter damage, not possible with DTI, and 3) comparison of gray matter and white matter damage. In addition, information derived from MT imaging will be complementary to DTI, as the former relies primarily on neuronal density and the latter on directionality [127]. FMRIB Software Library (FSL) [128] will be utilized for segmentation of gray matter from white matter for analysis of MT data, which will then be correlated with radiation field maps, perfusion and DTI data. Comparison will also be made to grading of gray and white matter damage on conventional imaging.

2.6.2 Diffusion-Tensor Imaging (DTI)

DTI is the most important magnetic resonance imaging technique to investigate brain white matter development and injury in vivo. Numerous lines of evidence support the use of DTI in studying treatment effects on brain structures composed predominantly of white matter tracts [129-132]. Animal histological studies demonstrated strong correlation between changes in DTI metrics and radiation-induced demyelination, axonal degeneration, and necrosis in the brain [119]. DTI metrics were also found to be significantly related to neurological deficits in patients [133-136]. Brainstem and cerebellar white matter pathways will be studied with DTI in this protocol due to their proximity to posterior fossa tumors and susceptibility to radiation injury. When craniospinal irradiation is delivered for patients with distant metastasis, supratentorial white matter tracts are likely to be affected and will be studied as well.

For ependymoma recurrent in the posterior fossa, white matter tracts in the brainstem and cerebellum are particularly vulnerable to therapy-induced injury.

Radiation dose delivered to these critical organs from previous radiation treatments often reach their tolerance estimated to be in the range of 54-60Gy [137]. Severe motor and sensory deficits could occur if irradiated fiber tracts have not been repaired sufficiently from prior irradiation at the time of second irradiation. We will perform baseline DTI studies prior to re-irradiation to evaluate the recovery status of brainstem and cerebellum white matter tracts. The results will be compared to age-related benchmark values previously obtained from healthy volunteer children. Serial DTI studies will also be performed at each follow-up visit to monitor the evolution of therapy-induced injury and recovery in white matter structural integrity.

For recurrent brain tumors, DTI can be helpful in assessing the tumor infiltration into the peritumoral white matter regions [138, 139]. DTI has also been used to differentiate recurrent brain tumors from radiation injury [140]. These potentials will be explored in this unique pediatric population. For normal tissue protection, changes in normal white matters adjacent to tumor or tumor bed due to surgical resection and reirradiation in children were rarely documented. Long term effects of re-irradiation on cerebral white matter development in children were not clearly understood. Serial DTI studies performed in this trial will be analyzed to answer above questions for reducing the knowledge gap. Collected DTI data will help estimate the radiation tolerance of cerebral white matters and the brain in children.

DTI will be acquired with a double spin echo EPI pulse sequence which applies diffusion-encoding gradients along 12 non-linear, non-coplanar directions in space. To facilitate comparisons with magnetization transfer imaging and previously acquired benchmark data in healthy children, examinations will be preferentially performed at 3T but may be performed at 1.5T if imaging at 3T is contraindicated. Each DTI study will contain 4 repetitions of the same diffusion pulse sequence to improve signal to noise ratio. These 4 imaging datasets will be spatially registered to a raw image dataset without diffusion gradient encoding (b=0) to correct for patient motion and linear system drift during acquisition before performing diffusion tensor calculation. Voxel-based DTI metrics which can be calculated for quantitative analysis include apparent diffusion coefficient (ADC), fractional anisotropy (FA), relative anisotropy (RA), parallel and perpendicular eigenvalues ($\lambda_{//}$ and $\lambda_{\perp}$). ADC and FA values represent the magnitude and directionality of water diffusion in each tissue voxel, respectively. ADC has the unit of mm^2/s. FA is dimensionless and ranges from 0 (isotropic diffusion) to 1 (highly directional). To determine if DTI reflects and predicts treatment toxicity, changes in these imaging metrics from serial DTI measurements will be correlated with results of longitudinal neurological outcomes and radiation dosimetry.

2.6.3 Dynamic Susceptibility Contrast-enhanced (DSC) Imaging

DSC MRI is a magnetic resonance imaging technique which quantifies blood perfusion in cerebral tumors and brain tissues by measuring the changes in relaxation time T_2* due to the signal dephasing associated with the susceptibility-induced gradients surrounding the paramagnetic contrast agent. It involves a rapid injection of a bolus of paramagnetic contrast agent into a vein following 1-2 min baseline data collection and the continuous tracking of the transient signal loss during the passage of the contrast agent through the tissue of interest. The dynamic data acquisition typically utilizes a heavily T2*-weighted sequence with a temporal resolution of 2 s or less. The more commonly used sequences are echo-planar imaging (EPI) and fast low-angle single-shot (FLASH) [141]. The latter sequence has less image distortions in regions of high magnetic susceptibility gradients such as tissue-air interfaces. Voxel-based DSC MRI metrics include relative cerebral blood flow (rCBF), relative cerebral blood volume (rCBV), and mean transit time (MTT). These derived DSC MRI metrics are often used for disease state characterization and therapeutic efficacy assessment [142-146].

In this protocol, we will focus on investigating radiation effects on perfusion of brainstem by examining relative differences in blood flow and blood volume between patients and longitudinal changes within the same subjects. These perfusion changes will be compared to diffusion changes in white matter tracts and to tests of neurological function to determine if therapy-induced perfusion and diffusion changes in brainstem can be detected before the manifestation of neurological signs and symptoms. DSC perfusion imaging is also clinically useful in differentiating between recurrent tumor and radiation necrosis. In such cases, and depending on the ability to perform a whole-brain examination, DSC perfusion imaging will require repositioning to center on the region of clinical interest.

2.6.4 Susceptibility-weighted Imaging (SWI)

This technique was originally developed to noninvasively assess the vascular architecture of brain parenchyma. The unique potential of SWI lies in its ability to exquisitely highlight vascular structures based on differences between magnetic susceptibility in blood (BOLD effect) and surrounding tissues. SWI also has the potential to detect, and perhaps even quantify extremely small amounts of magnetically susceptible substances within brain parenchyma and thereby detect the presence of microscopic hemorrhages. Potential uses of SWI include tissue characterization through visualization of architecture within brain lesions and monitoring such susceptibility changes as an indicator of treatment response or disease progression. SWI also allows detection of small amounts of blood degradation products that would otherwise not be detectable at imaging. This aspect of the technique may permit early detection of radiation induced vascular changes within the brain, such as venous anomalies and associated cavernous malformations, and possibly allow prevention of hemorrhagic complications from these lesions.

2.7 Rationale for ^{18}F-Fluorodeoxyglucose and ^{11}C-Methionine PET to Detect Ependymoma and Monitor Response to Radiation Therapy

Because ependymoma is amenable to imaging using to positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) or ^{11}C-methionine (MET, both of which are under study for the evaluation of brain tumors for the purposes of detection, staging and monitoring response to treatment, PET has tremendous potential and value in evaluating residual or recurrent disease and radiation necrosis. We have demonstrated that ependymoma is avid to FDG. We will explore the utility of FDG and other compounds to image residual tumor and investigate whether the level of avidity before treatment correlates with tumor progression after a second course of irradiation or may be used to differentiate between tumor progression and radiation necrosis. Knowledge of the limitations of this modality will enhance or curb its use. Although it may be difficult to define boundaries using PET because of its resolution, it may be useful to define some aspects of the tumor volume for targeting because local failure is the principal mode of failure.

Ependymoma is a tumor found within the CNS and should be amenable to positron emission tomography with ^{18}F-fluorodeoxyglucose or ^{11}C-methionine (IND # 104987), both of which are under study for the evaluation of brain tumors for the purposes of detection, staging and monitoring response to treatment. We have demonstrated that ependymoma is avid to FDG and will explore the utility of FDG and other compounds to imaging visible residual tumor, differentiate between tumor and necrosis, and investigate whether the level of avidity 12, 24 and 36 months after irradiation correlates with tumor progression. Knowledge of the limitations of this modality will enhance or curb its use. Although it may be difficult to define boundaries using PET because of its resolution, it may be useful to define some aspects of the tumor volume using PET because local failure is the principal mode of failure.

2.8 Growth Factor and Cytokine Responses to Radiation Therapy

Our previous work in patients with the brain tumors (ependymoma and low-grade glioma) and pediatric soft-tissue sarcoma (Ewing sarcoma, rhabdomyosarcoma and non-rhabdomyosarcoma soft-tissue sarcoma) has shown that cytokine and growth factors levels measured in serum before, during and after radiation therapy correlate with clinical factors, tumor types and disease control [147-149]. Levels of pro-inflammatory cytokines have been used to predict side effects in normal tissues after radiation therapy, monitor tumor and normal tissue responses to treatment, and demonstrate the differences between tumor and normal tissue responses where the latter serves as an indicator of the systemic effects of irradiation. Serum cytokines also appear to correlate with disease groups, patterns of treatment and the volume of residual disease in patients with soft-tissue tumors. Growth factor and cytokine responses to irradiation will be measured and modeled to investigate associations between their levels and disease control and side effects that exist for patients with craniopharyngioma. On treatment

monitoring will allow us to explore associations between growth factors and cytokines and cyst formation. Monitoring after treatment will help us to study the systemic nature of the radiation response and the correlation with neurological, endocrine and cognitive/quality of life parameters.

Cytokines are hormonal messengers responsible for modulating biological effects in normal tissues and the immune system. They can be divided into two groups: those that are proinflammatory (Th1 cytokines) and those that are anti-inflammatory (Th2 cytokines). Th1 cytokines perpetuate autoimmune responses, promote tissue damage and may be responsible for fatigue and promoting chronic diseases [150-153]. Th2 cytokines have anti-inflammatory effects and may balance Th1 responses. Diseases resulting from excess inflammation may be prevented through a variety of means; therefore, understanding changes in cytokines after irradiation may provide opportunities for secondary prevention. We will investigate the possible correlation between the change in cytokine levels and factors such as radiation dose and irradiated volume, time since irradiation, tumor volume, tumor response, surgical and host factors, etc. We will also evaluate the association between cytokine responses and measures of sleep, fatigue and function. The actual volume of blood for the cytokine studies is 6 ml per time point. There are eight time points: baseline, weeks 3 and 6 of radiation therapy and 5 additional time points during follow-up.

2.9 Rationale for Genomic Analysis of Untreated and Recurrent Ependymoma and Evaluation of Host Factor Susceptibility to Treatment-Related Side Effects

By identifying genetic predictors of neurotoxicity in ependymoma patients before irradiation it will be possible to recognize those individuals who are most vulnerable and alter their medical management and follow-up. By focusing our research inquiry on a homogenous sample of patients, that is, patients with ependymoma who have the similar tumor pathology and treatment, we can examine the multiple factors that contribute to outcome that may have implications for other, less common, brain tumors in children as well as other pediatric malignancies. There is significant inter-individual variation in neuro-toxicity in brain tumor patients [154-156].

This variation is likely related to the many variables that influence outcome. Factors that may influence outcome can be divided into *tumor* (presenting symptoms, tumor size, tumor location, pathological/molecular type), *treatment* (extent of resection, repeat surgery, radiation dose and dosimetry, chemotherapy, time since treatment), *host* (age at diagnosis and treatment, gender, genetic determinants), and *environment (*socio-economic status) related predictors. For example, larger tumor size, greater medical complications following initial surgery, higher radiation dose and larger treated volume, younger age at diagnosis, and longer time since treatment all predict for neuro-cognitive deficits and white matter damage [25, 157, 158]. Other factors that may influence outcome are not known prior to treatment and/or may be confounded with

treatment. To take the next step in predicting outcome and use this knowledge for individualizing and optimizing therapy in order to reduce late effects it is important to identify those variables that we can assess prior to – or at least very early in - the medical management of children with recurrent ependymoma. For example, patient age is already considered in decisions regarding the use of cranial radiation because of the particular vulnerability of the very young brain [159]. In order to further modify treatment in the most vulnerable patients and ensure early intervention, biomarkers of outcome that can be obtained early following diagnosis are necessary. Variability in outcome is likely due in part to genetic variation in individuals that renders them especially susceptible or resilient to injury. Delineating genetic markers that identify individuals at risk or resilient to treatment induced toxicity provides the foundation for maximizing individualized treatment de-escalation and targeting neuro-protection. We will therefore, perform selective candidate gene analysis to define patients at risk neurocognitive and other clinical aspects of radiation induced neurotoxicity. We will perform this using germline gene SNPs and analysis of peritumoral normal brain tissue for specific damage. From the candidate genetic markers we will evaluate will be prioritized within two categories. As a first priority we will examine markers known to predict the physiological response to treatment for cancer and vulnerability to toxicity Genes [160] have been identified where polymorphisms are related to toxicity following treatment with radiation for brain tumors, including intellectual impairment [161]. Polymorphisms in the ATM, TGFB1, CYP2D6, LIG4, XRCC1, XRCC3, hHR21 genes have been shown to be associated with an increased risk of developing an adverse reaction to radiotherapy in normal tissue [162-165]. In general, cytokines or genes involved in DNA repair and apoptosis may be involved in toxicity response to radiation. As a secondary priority we will also examine genetic markers associated with brain integrity and vulnerability to neuronal insult which may predispose an individual to greater toxicity following treatment. High resolution genomic assays have been used to reveal novel genes and other complex genetic abnormalities (i.e., ASAH1, PTCHD1, CDH8, MBD5, SHANK2, MACROD2) associated with intellectual disability, neuro-developmental disorders and cognitive deficits [166-170]. Such predictors of overall cognitive function may help determine which patients will do better or worse following treatment. Likewise, genetic anomalies associated with white matter disease, neuro-degenerative disorders, and response to brain injury [162-165] may be useful in predicting patients vulnerable to late effects of treatment for recurrent ependymoma. We will also assess normal tissue for evidence of DNA damage, vascular insufficiency and damage [171, 172] and for expression of any of the “protective candidate genes”.

2.9.1 Biological Correlates of Vasculopathy, Hearing Loss, Cognition Effects, Growth Hormone Deficiency and Disease Control.

Normal blood samples will be acquired by protocol collaborators prior to initiation of treatment. Germline will be isolated and analyzed by SNP microarrays and re-sequencing analysis in conjunction with tumor specimens in

order to pinpoint the genetic events occurring during tumor initiation and development. Since the analyses of these samples won't take place for at least 5-6 years from the initiation of enrollment, it is likely that substantial changes will take place in available technology to process the samples as well as in methods to analyze the data. Further additional insights in the biology of these tumors may become available which may influence the analyses to be performed. Therefore it is not possible to state precisely the types of analyses which will be pursued.

The goal of radiogenomics is to identify genetic variations that predict for side effects from radiation therapy with the long-term aim of screening susceptible patients prior to irradiation and to study the biology of late effects. Assays to predict radiosensitivity developed in the past have not been useful nor have they been easy to implement in the general population including in children. The ability to assess genetic variation through the evaluation of single nucleotide polymorphisms has been considered a breakthrough and reasonable entry point from which to collect information to study inherent radiosensitivity. This has been successful in the study of radiation-related effects in adult patients with breast and prostate cancer, and it is considered one of the key steps in delivering limited-toxicity personalized medicine to children with cancer. Our track record of treatment and follow-up, annotation of patient specimens, consistency of care and the number of patients included in this study will increase the likelihood that such an association may be detected, if it exists. Genomic studies will be performed to evaluate constitutional DNA from whole blood samples. The goal will be to evaluate the latent systemic effect of radiation therapy. Our objective is to investigate which genetic polymorphisms may be associated with radiation-related side effects in children. Some specific approaches to addressing this objective are outlined below. This list is not exhaustive, however, and at the time of analysis, additional insights may be available which could change the direction of and approach to these analyses. Clinical genomics testing may be ordered for all patients including germ line testing. The data may be used to explore the associated outcomes outlined in this protocol document. In the setting where there is insufficient tumor available for clinical genomics, the patient may be scheduled for genetics counseling with the appropriate clinic at which time germ line testing alone may be ordered. The data obtained from this route of germ line testing may be used to explore the associated outcomes outlined in this protocol document.

2.9.2 Genetic Abnormalities Associated with Vasculopathy

Pediatric stroke has a variety of presentations, including headache, seizure and acute neurological deficits including hemiparesis. There are several gene-specific disorders with a significantly high predisposition for stroke including sickle cell disease (SCD), homocystinuria, progeria, and neurofibromatosis.

It is known that the predisposition for stroke is related to the HgS genotype in SCD [173], however, other candidate genes that may play a role in stroke susceptibility have been identified in this population [174]. Children with SCD

were phenotyped into large-vessel (LV) and small-vessel (SV) stroke subgroups by magnetic resonance imaging and angiography and genotyped for polymorphisms associated with blood pressure regulation, cellular adhesion, inflammation, and lipid metabolism. Polymorphisms in IL4R, TNF, and ADRB genes were associated with stroke risk in the LV subgroup, while VCAM-1 and LDLR gene polymorphisms were associated with SV stroke risk, suggesting a basis for which population screening and targeted intervention may aid in the prevention of stroke in SCD patients.

A number of candidate genes that may contribute to pediatric stroke in the general pediatric population have also been identified [175]. Polymorphisms in genes underlying thrombophilia (Factor II, Factor V, MTHFR, and PAI-1) appear to be risk factors for venous sinus thrombosis and arterial ischemic stroke [176]. More recently, a polymorphism within the promoter region of the GPx-3 gene that compromises plasma antioxidant and antithrombotic activities was identified as a risk factor for arterial ischemic stroke in children and young adults [177].

The majority of gene identification for intracranial aneurysm (IA) risk has been performed in adults. One candidate gene that may contribute to IA is the elastin (ELN) gene, a major component in the blood vessel wall. Researchers showed that the presence of the Mm INT20/INT23 haplotype occurred more frequently in patients with IA compared to controls [178]. The collagen α2(I) gene [179], important for vascular wall elasticity, may also serve as a candidate gene for IA risk as the Ala459Pro SNP was observed with higher frequency in familial IA patients [179]. The TNFRSF13B gene encodes a TNF receptor that plays a role in inflammation. Single nucleotide polymorphisms identified within the TNFRSF13B gene were associated with IA, suggesting that TNFRSF13B may also serve as a candidate gene for IA susceptibility [180].

One study attempted to identify genes that were associated with aneurysms (though not intracranial) in children. In children with Kawasaki disease, coronary artery aneurysms will develop if untreated. Researchers identified an SNP within the inositol 1,4,5-triphosphate 3-kinase C [181] gene associated with Kawasaki disease susceptibility and formation of coronary artery aneurisms in both Japanese and US children [181].

Moya-moya syndrome is defined as bilateral severe stenosis or occlusion of the internal carotid arteries with collateral formation [182]. The same Moya-moya-type *appearance* is seen in a number of vastly different clinical settings including sickle cell disease, neurofibromatosis, Down syndrome, Morning Glory abnormality, and post-irradiation. The common underlying pathophysiology has yet to be clearly elucidated. To determine the pathogenesis of Moya-moya, children and adults were angiographically confirmed for Moya-moya then human leukocyte antigen (HLA)-serotyped [183]. Their results showed that Moya-moya was associated with HLA-AW24, -BW46, and -BW54 serotypes.

2.9.3 Genetic Abnormalities Associated with Hearing Loss

Nonsyndromic hereditary impaired hearing (NSHIH) accounts for 60-70% of congenital impaired hearing [184]. A disorder restricted to the ear and vestibular system (as opposed to syndromic HIH which may occur as part of a multisystem disease), NSHIH is caused almost exclusively by cochlear defects, resulting in sensorineural hearing loss. There are a number of gene mutations that contribute to NSHIH (Table 1) [184]. Mutations of the GJB2 gene are the major cause of NS autosomal recessive and sporadic deafness [185] and are ethnic-specific. The most frequent mutation observed in patients with European ancestry is 35delG [186], while 235delC occurs most frequently in the Japanese population [187]. Aminoglycoside antibiotics, such as gentamycin, streptomycin, and tobramycin, are widely used to treat gram-negative bacterial infections. Aminoglycosides are well-known for their dose-limiting effects on hearing loss [188]. Studies have shown that some people have a genetic predisposition that renders them extremely sensitive to the ototoxic effects of aminoglycosides [189]. Mutations in the mitochondrial 12S ribosomal RNA gene account for most cases of aminoglycoside-induced ototoxicity with A1555G occurring most frequently [190]. Due to the high frequency of this mutation, as well as GJB2, researchers have developed a molecular screening test for these genes to aid in the early identification of hereditary hearing loss and genetic susceptibility to aminoglycoside-induced ototoxicity for the Chinese population [191].

There have been a few attempts to identify associations between hearing gene mutations and cancer treatment-induced ototoxicity in patients. Cisplatin is often used to treat pediatric solid tumors, but one of the dose-limiting side effects is sensorineural hearing loss [192]. To test whether mutations in genes responsible for cisplatin detoxification contribute to cisplatin-induced ototoxicity, cisplatin-treated testicular cancer survivors were retrospectively assessed for functional polymorphisms in genes coding for glutathione S-transferase enzymes [193]. Their results indicate that SNPs within the GSTP1 gene contributed to cisplatin-induced ototoxicity and suggest that the GSTP1 gene may impact an individual's susceptibility to cisplatin-induced ototoxicity. Another study sought to test whether there was an association between cisplatin-induced ototoxicity and megalin mutations [194]. Megalin is an endocytotic receptor that has been associated with the uptake of aminoglycosides which are similar to cisplatin in their ototoxic effects. Patients who did and did not develop hearing loss after cisplatin treatment were analyzed for megalin SNPs. Their results demonstrate that SNPs within the megalin gene occurred at a higher frequency in those patients who developed hearing loss after cisplatin treatment and suggest that the megalin gene may impact an individual's susceptibility to cisplatin-induced ototoxicity.

In contrast, one study showed no association between hearing genes and susceptibility to cisplatin-induced ototoxicity [195]. Using buccal washes from 11 children who developed hearing loss after cisplatin treatment, the authors

performed retrospective mutation screening of GJB2, SLC26A4, MTRNR1, MTTL1, and MTTS1 but found no association. However, there are weaknesses in this study: 1) small cohort and 2) method of patient selection which was based on self-reported hearing loss with no audiometric measurement. The authors state that the lack of an association may also be confounded by the large number of survivors in whom deafness may have been more a function of the tumor or radiation therapy than of cisplatin treatment.

In our own experience, we understand that hearing loss is uncommon and predictable in patients with craniopharyngioma when baseline hearing is normal. Among 75 children with craniopharyngioma followed longitudinally with audiograms that we reviewed for hearing loss in preparation for this protocol, we identified 2 with pre-existing hearing loss (intermediate and high-frequencies) that could not be attributed to known clinical or host factors.

2.9.4 Genetic Abnormalities Associated with Cognitive Deficiencies

The polygenic nature of cognitive ability has made it difficult to identify specific genes underlying normal cognition; however, nonsyndromic mental retardation (NSMR) may serve as the best example from which to assess genes involved in cognitive deficiencies since similar conditions are associated with purely cognitive phenotypes and are not secondary to other abnormalities that constitute a particular syndrome.

A number of genes have been identified that appear to play a role in NSMR (Table 3) [196]. Three genes are involved in Rho GTPase signaling: GDI1, oligophrenin, and PAK3. GDI1 encodes a guanine nucleotide dissociation inhibitor which prevents the deactivation of a small GTP-binding protein that plays a role in synaptic vessel recruitment for exocytosis. Oligophrenin is a rhoGAP protein that stimulates the intrinsic GTPase activity of certain small G proteins. PAK3 encodes p21-activated kinase which links Rac to Cdc42 and to transcriptional activation. Altogether, mutations in any of these genes may disrupt the normal development of axonal connections or compromise synapse function [197]. Other genes shown to be involved in NSMR include FMR2, IL1RAPL, TM4SF2, VCX-A, and ARHGEF6, all of which can lead to neuronal dysfunction if mutated [197]. More recently, polymorphisms of GPC3, GPC4, and HTR2A genes were identified in families with NSMR [198].

Another gene that may contribute to normal cognition is the SNAP-25 gene. SNAP-25 encodes a presynaptic terminal protein important for regulation of neurotransmitter release from neurons with high expression in the hippocampus, a brain structure central to learning and memory processes. One study genotyped children and adults with variable IQ phenotypes for SNAP-25 SNPs and found 4 SNPs in intron 1 of the SNAP-25 gene that were significantly associated with IQ which suggests that functional polymorphisms within noncoding regulatory

sequences may also be associated with expression of genes underlying cognitive function [199].

There is a disorder associated with severity-dependent changes in cognitive ability known as obstructive sleep apnea (OSA). Since the severity of OSA accounts for only 40% of the variance in cognitive performance, researchers have sought to determine if there was a genetic determinant of individual susceptibility that may contribute to cognitive dysfunction [200]. The APOE gene encodes apolipoprotein E, a lipoprotein that may have neuroprotective and anti-inflammatory effects in the brain [201]. Adult patients with OSA displayed more severe cognitive dysfunction when the APOE ε4 allele was present than those patients with other APOE alleles. To test whether the presence of the APOE ε4 allele accounted for increased cognitive dysfunction in children, children with OSA were genotyped for the ε4 allele [200]. Their data showed that the frequency of the ε4 allele was higher in children with OSA, particularly in those children with cognitive deficiencies. These data suggest that not only is the presence of the APOE ε4 allele associated with increased risk for OSA, but also with increased risk for cognitive dysfunction.

The neurocognitive effects of cancer treatment can markedly impact QOL in children with cancer, but it is not known why some children fare worse than others. To date, there are few studies that have attempted to identify genes that may contribute to cognitive dysfunction susceptibility in these children. Because the chemotherapeutic agent methotrexate (MTX) contributes to cognitive dysfunction via homocysteinemia, one such study attempted to test whether polymorphisms in genes responsible for maintenance of homocysteine levels contributed to cognitive decline in children treated with cranial irradiation (CI) for acute lymphoblastic leukemia (ALL) [202]. Their results showed that IQ decline was apparent among children with the NOS3 (endothelial nitric oxidase synthase) 894TT genotype who received CI, suggesting that NOS3 may serve as a predictor for children that are susceptible to cognitive decline following radiation therapy.

Investigators at St. Jude have assessed the relationship between dopamine and the dopamine degrading enzyme Catechol-O-Methyltransferase (COMT), changes in frontal brain white matter and the effects of CNS directed therapy including children treated with focal irradiation [203]. They found that patients with the Met/Val genotype performed significantly better in tests of executive function than those with the Val/Val or Met/Met genotype suggesting that COMT genotype is associated with working memory performance and may indicate resiliency against late effects.

2.9.5 Genetic Abnormalities Associated with Hormone Deficiencies

Gene polymorphisms that may be associated with response to treatment and toxicity are under investigation to discriminate between individuals at risk for endocrine effects of cancer therapy including radiation therapy. The roles of

glutathione S-transferase enzymes, which detoxify normal tissues, are viewed as key molecules for the role that they play in oxidative stress. Genetic aberrations in GST (GSTM1, GSTP1, GSTT1) increase the risk of relapse of certain cancers and modulate response to therapy [160]. Pediatric investigators in New South Wales have shown that children age less than 14 years with a null allele for GSTM1 who undergo radiation therapy may have increased susceptibility to growth hormone deficiency. Considering that there may be an important proportion of children with this type of genetic make-up and that even low-dose hypothalamic irradiation [204] will ultimately result in growth hormone deficiency, testing the hypothesis that GST deficiency modulates growth hormone in children would be both feasible and rewarding. Treatment with glutathione has been shown to confer a neuroprotective effect against neurotoxic chemotherapy such as oxaliplatin [146].

2.10 Pathology and Biological Studies

Pathological evaluation will be used to confirm the diagnosis of ependymoma and, therefore, patient eligibility, but beyond this the collection of tumor material as part of the present trial represents an opportunity to study several aspects of the pathology and biology of both primary and recurrent ependymomas.

No reliable prognostic or predictive biomarker currently exists for the therapeutic stratification of ependymoma; even the clinical utility of the WHO pathological classification of this tumor is controversial. However, recent studies at St. Jude and elsewhere have begun to reveal molecular abnormalities in ependymoma that might serve either as outcome indicators of disease or as targets for 'small molecule' therapies. In particular, genomic analyses have revealed both key recurrent molecular alterations in supratentorial ependymomas and molecular subgroups among both supratentorial and infratentorial tumors. Supratentorial ependymomas form two molecular subgroups, with tumors characterized or not by a *C11orf95-RELA* fusion gene; approximately 70% of supratentorial ependymomas harbor this fusion gene, which is associated with up-regulation of the NF-κB pathway, a potential therapeutic target [205]. Posterior fossa ependymomas also form two molecular subgroups [206], and data from this first study suggest that the two subgroups have distinct genetic alterations and outcomes. St. Jude data on childhood posterior fossa ependymomas also suggest that there are two molecular subgroups [207].

Aim 1. Anecdotal evidence suggests that ependymomas may or may not show increasing signs of histologic anaplasia upon recurrence, but a detailed analysis of histologic features in paired primary and recurrent tumors has not been previously undertaken. In addition to standard indices of anaplasia - tumor cell density and nuclear pleomorphism, mitotic count, microvascular proliferation, and necrosis, the presence or absence of tumor cell invasion into adjacent parenchyma will be evaluated in formalin-fixed paraffin-embedded (FFPE) sections from primary and recurrent tumors. Pathological features will be related to several clinical indices: site of recurrent disease - local or metastatic, progression-free interval, and

outcome.

Aim 2. We have developed assays to determine molecular subgroup from FFPE material. The presence or absence of a *C11orf95-RELA* fusion gene in a supratentorial tumor can be detected by interphase fluorescence *in situ* hybridization (iFISH) in FFPE tissue sections [205], while the two posterior fossa ependymoma subgroups can be detected by a Quantigene assay using RNA extracted from FFPE sections [207]. Molecular subgroup will be determined for primary and recurrent disease to test the hypothesis that molecular subgroup does not change with tumor recurrence, as is the case for medulloblastoma [208]. In addition, associations between molecular subgroup and the following clinicopathological variables will be sought - site of recurrent disease - local or metastatic, PFS, and outcome.

2.11 PET Activation

We will investigate the feasibility of using post-treatment PET as an in-vivo dosimetric, distal edge, and linear energy transfer (LET) verification system for pediatric patients with ependymoma. Factors that may limit the practicality of this system are loss of signal intensity due to activation decay of relevant isotopes and loss of resolution due to biological washout and patient motion. Conventional radiation therapy uses X-rays to deposit dose within a patient. Dose deposition occurs predominantly through photon-electron interactions in tissue. Proton therapy uses a subatomic particle known as a proton. Protons also interact with electrons in tissue to deposit dose; however, because of their physical characteristics, protons have a significant probability of interacting with atomic nuclei. During proton therapy it is possible to convert stable ^{16}O, ^{14}N and ^{12}C atoms within tissue to the short-lived positron emitters [209] ^{15}O, ^{13}N and ^{11}C. These positron emitters (primarly ^{11}C) can be imaged using a clinical PET [210, 211] system. A correlation between the dose deposited by protons and the PET image can be obtained via Monte Carlo simulations[212], leading to in-vivo dosimetry and distal edge verification of the proton beam. Based on the decay characteristics of the activated isotopes, PET imaging after multiple sequential treatment beams may not adequately image the beam path of the earliest beams in the series. Methods have not been fully developed to separate the contribution of multiple beams in activation imaging. To remedy these uncertainties, activation studies will be limited to individual beam measurements.

3.0 ELIGIBILITY CRITERIA AND STUDY ENROLLMENT

According to institutional and NIH policy, the study will accession research participants regardless of gender and ethnic background. Institutional experience confirms broad representation in this regard.

3.1 Inclusion Criteria

- Progressive intracranial ependymoma after prior focal irradiation
- Patients aged 1-21 years at the time of enrollment
- Adequate performance status (ECOG < 3) and research participant does not require mechanical ventilation
- Interval from start of initial radiation therapy to enrollment > 9 months

3.2 Exclusion Criteria

- Prior craniospinal irradiation
- Pregnant women are excluded from enrollment on this study because radiation therapy is an agent with the potential for teratogenic or abortifacient effects
- Any patient with both metastatic ependymoma and age < 3 years at the time of enrollment

3.3 Recruitment

The statistical design of this trial requires that 90 eligible patients be enrolled over a 9 year period. Accounting for ineligible patients, which are expected to be at most 10%, the total number of patients to be accrued to this study may be 99. We expect to enroll about 12 patients per year for approximately 9 years. The study will enroll patients with ependymoma and progressive disease. There is no exclusion to enrollment based on the time interval between initial tumor progression and enrollment. In the event that the accrual of patients is slower than expected, we will consider collaborating with other centers that specialize in the treatment of ependymoma. Patients with a prior history of radiosurgery may be excluded from protocol enrollment if the principal investigator or his designee determines that the risk of injury associated with fractionated retreatment is excessive.

3.4 Enrollment on Study

A member of the study team will confirm potential participant eligibility as defined in Section 3.1-3.2, complete and sign the 'Participant Eligibility Checklist'. The study team will enter the eligibility checklist information into the Patient Protocol Manager (PPM) system. Eligibility will be reviewed, and a research participant-specific consent form and assent document (where applicable) will be generated. The complete signed consent/assent form(s) must be faxed or emailed to the CPDMO at 595-6265 to complete the enrollment process.

The CPDMO is staffed 7:30 am-5:00 pm CST, Monday through Friday. A staff member from the Milli helpline is on call Saturday, Sunday, and holidays from 8:00 am to 6:00 pm. If you have a therapeutic research enrollment and need assistance releasing your consent, please call the Milli helpline (901-338-0596) on call number.

3.5 Enrollment Instructions for Collaborative Sites

Collaborating Site research participants should be registered at St. Jude within 72 hours of enrollment at the site. The completed Eligibility Checklist and entire signed Informed Consent should be faxed to 901-595-6265. Please call 901-595-2568 if confirmation of the enrollment information is needed. The Protocol Eligibility Coordinator will then register the research participant in the St. Jude CTMS.

4.0 TREATMENT AND PLAN STRATIFICATION

4.1 Overview

Patients will be enrolled on this protocol at St. Jude Children's Research Hospital (SJCRH) if they meet the eligibility criteria outlined in section 3.0. Patients may be enrolled before or after surgery performed at the time of recurrence. Enrollment prior to surgery is preferred to prospectively obtain peri-operative information about surgical morbidity and to facilitate the acquisition of tissue for biology studies. This protocol allows for co-enrollment on other protocols for recurrent ependymoma including those that might administer chemotherapy after irradiation. Chemotherapy concurrent with radiation therapy will not be allowed. Patients will be jointly evaluated by treatment teams representing neuro-oncology, radiation oncology and neurosurgery.

In the event that collaborative sites are allowed to join this trial, SJCRH will not be financially responsible for the cost of surgery, radiation therapy or follow-up for patients enrolled at collaborative sites. All patients are expected to undergo clinically indicated follow-up measures at the enrolling institution or at their routine point of care. Collaborative sites are expected to perform the research outlined in the protocol unless otherwise specified. The PI and protocol team at SJCRH will establish appropriate and legal (HIPAA) compliant communication with the enrolling institutions and the routine point of care for each patient.

Patients will be considered for enrollment if they have progressive disease after prior therapy that included surgery and focal irradiation with or without chemotherapy. There is no limit regarding the time interval from initial treatment failure to enrollment on this protocol which means that patients may choose other forms of therapy prior to enrollment on this protocol. Multiple episodes of progression will be allowed. The most common enrollment scenario will be the

patient who has been diagnosed with asymptomatic recurrence noted on surveillance neuroimaging. This patient will be consented for the study and will undergo pre-operative evaluations. Post-operatively, the studies necessary for treatment planning and to assess the impact of resection will be performed or repeated.

It is expected that some patients will have surgery for local recurrence or metastasectomy prior to enrollment. Enrollment before surgery is preferred to facilitate tumor-related imaging studies, tissue procurement and baseline evaluation of neurological function. Regardless, studies performed prior to enrollment and tissue from any surgery performed prior to enrollment will be part of the protocol data set.

Patients will be enrolled if initial or post-irradiation pathology or imaging reports confirm a diagnosis of ependymoma or suggest a differential diagnosis that might include ependymoma. Limited tissue availability from initial and subsequent surgeries along with expanding efforts to sub-classify tumors may lead pathology reviewers to consider a range of diagnoses for which identical interventions and treatments would be considered. These patients will be enrolled after review by the principal investigator and treating physicians.

At the time of enrollment, patients will undergo extent of disease evaluation that will include MR imaging of the brain and spine and CSF cytology. To reduce cost and in consideration of the patient, the extent of disease evaluation may be waived with PI approval if a similar and adequate evaluation was performed within 3 weeks of enrollment. It should be noted that for patients who proceed directly to irradiation, specific sequences will be required for radiation therapy treatment planning of intracranial disease if not present in the prior extent of disease evaluation. For patients who undergo further surgery, extent of disease evaluation after surgery is required; only CSF cytology may be waived based on safety concerns or for patients with obvious neuraxis metastases noted on imaging.

Optimally, patients will undergo surgery to achieve minimal residual disease. It is our hope, but not required, that they will experience limited morbidity from surgery and proceed to irradiation within 12 weeks of last surgery. The pre- and post-operative neuroimaging and clinical assessments will be completed to satisfy the secondary objectives for the study, aid in the treatment planning process, and provide information for longitudinal assessment of toxicity.

Surgery performed prior to registration will not preclude enrollment and treatment on this protocol but does limit the toxicity assessment which will be retrospective with regard to the pre-operative baseline. Resection prior to enrollment will also limit the imaging evaluation because not all patients will have, preoperatively, the MR sequences that are specified for longitudinal follow-up. We would hope that patients enrolling on the study prior to surgery will have the protocol-specified clinical and neuroimaging evaluation.

Occasionally, surgery may not be feasible or the patient and their parents will refuse. These patients should have a small volume of residual tumor. Although it is preferable to perform surgery to achieve minimal residual disease and acquire tissue for correlative analysis, surgery will be recommended, but not required. A general guideline is that the thickness measurement of residual disease should not exceed 5mm.

Neuraxis staging is commonly performed when patients are suspected to have recurrent tumor and prior to surgery; however, if neuraxis staging is not performed before resection of recurrent tumor, the patient will be eligible, because the same staging procedure will be recommended prior to the initiation of radiation therapy on this study.

Resection undertaken in a previously irradiated patient is difficult and significant morbidity may result. The intent of the protocol is to document operative morbidity clinically and by neuroimaging. There is no required time interval from the time of surgery to the initiation of radiation therapy. This will provide for a period of recovery for injured patients and assessment of performance status and morbidity factors that would make re-irradiation potentially dangerous or increase the risk of necrosis. Neurological evaluation and performance status assessment will be required. When surgical morbidity is significant and the patient is made ventilator dependent, unresponsive or there is no prospect for a meaningful recovery, they will be removed from study.

Neuroimaging review is required to proceed with treatment. Pathology review is required to centrally confirm the diagnosis and compare the recurrent tumor grade to that documented at the time of initial diagnosis. Patients cannot proceed with enrollment on this study unless sufficient records of prior irradiation can be obtained. Electronic records of prior irradiation (imaging and objects) will be requested with the help of the patient and their family. In the absence of electronic data from the initial course of radiation therapy; hard copy data will suffice provided a review is conducted by the PI and approved. The most common commercial planning systems will be available to the PI and other software or methods to electronically import treatment planning data for the evaluation of treatment and normal tissue effects. Tissue is strongly recommended to achieve the biology goals of the study. Tumor tissue from the initial surgery, recurrence(s) and any other time points will be acquired for biological evaluation.

4.2 Surgery

In addition to a detailed history along with physical and neurologic examinations, the preoperative evaluation should include, when appropriate, ophthalmologic examination, including visual field assessment and endocrinology consultation. Preoperative imaging should include a MRI of the brain.

The goal of surgical intervention should be to improve tumor control with minimal morbidity. Common indications for surgical intervention directed at the tumor will include establishing a tissue diagnosis and tumor control by radical resection.

Beyond the need to establish a diagnosis of recurrent ependymoma, patients will be selected for surgery based on the neurosurgeon's assessment that a GTR or meaningful resection may be achieved with acceptable postoperative morbidity. This protocol does not dictate the extent or type of surgery. This decision will be left to the treating neurosurgeon and the patient and parents or guardians following a discussion about the risks and benefits of surgery. It is recognized that in certain cases, the feasibility of radical surgery may initially require exploration. Patients who have been treated at other institutions will commonly undergo surgery prior to learning about this protocol. In some cases the extent of resection will be in determinant and the details of surgery vague. Because of the impact of radical surgery on outcome, we advise exploration, resection and wall biopsies where feasible to clearly define the extent of resection. Patients will be characterized as having undergone GTR based on an assessment of pre- and post-operative imaging and the report from the neurosurgeon.

An important exploratory objective of this protocol is to evaluate the impact of surgery on disease control and functional outcomes. Neurologic, endocrine, and functional outcomes as discussed in previous sections will be assessed at study enrollment and again after surgical intervention. Disease control will be monitored as discussed in previous sections, and factors affecting surgical outcomes will also be monitored. These will include previous surgical procedures, extent of disease, tumor location and tumor related effects including hydrocephalus and CSF shunt status.

Other surgeries not directly on the tumor but related to the disease will include CSF diversion procedures for hydrocephalus. Complications related to these surgeries will also be tracked. Surgical planning discussion for a patient with recurrent ependymoma will include a frank discussion of the risks and benefits of radical surgery.

Surgery to resect residual tumor during the first 12 months after the initiation of radiation therapy is allowed when the same residual tumor was present at the initiation of radiation therapy. There are instances when residual tumor, present and deemed unresectable at the initiation of radiation therapy, is observed to coalesce and become more demarcated as a result of treatment. This should not be misinterpreted as disease progression, which is highly unusual during the first few months after radiation therapy. Advice should be sought from the principal investigator. Likewise, during this time, viable residual tumor in the specimen does not constitute disease progression. Examples include non-enhancing residual tumor that enhances after radiation therapy, residual tumor more apparent on T2-weighted MR imaging after treatment, tumor adjacent to the brainstem or

involving the cerebellar peduncles or within the internal auditory meatus becoming more apparent after treatment. The same principles have been applied in recent front-line studies for ependymoma.

4.3 Stratification for Treatment

Stratification for treatment of ependymoma will be determined when radiation therapy planning is initiated. There is no limit to the number of participants in each stratum.

Stratum 1 (initial pattern of failure is local); disease confined to primary site; age >12 months at time of enrollment to < 21 years. Treatment: focal irradiation.

Stratum 2 (initial pattern of failure is metastatic); neuraxis metastatic disease without equivocal evidence of local failure; age > 36 months at time of enrollment to < 21 years. Treatment: craniospinal irradiation.

Stratum 3 (initial pattern of failure is both local and metastatic): neuraxis metastatic disease with unequivocal evidence of local failure; age > 36 months at time of enrollment to < 21 years. Treatment: craniospinal irradiation.

Stratum 4 (initial pattern of failure is local): disease confined to primary site; age >36 months at time of enrollment to < 21 years; tumor shows presence of 1q gain. Treatment: craniospinal irradiation (optional).

4.4 Radiation Therapy

Radiation therapy will be started once a final treatment plan has been developed and approved. There is no time limit for the interval from enrollment to when irradiation commences.

4.5 Chemotherapy

The use of chemotherapy prior to or after re-irradiation will be allowed for patients enrolled on this study. The use of chemotherapy during the initial management of ependymoma has become more commonplace as investigators seek to determine the role of chemotherapy for patients with initially unresectable ependymoma [213] or in patients after gross-total resection [214]. The impact of chemotherapy on disease control and complications will be considered in the statistical design. It is envision that as combined modality therapy becomes more common for children, with ependymoma, the novel agents [215] tested in conjunction with re-irradiation will vary over time and according to specific clinical and biological parameters.

5.0 RADIATION THERAPY GUIDELINES

5.1 General Guidelines

Radiation therapy on this protocol will be based on extent of disease, extent of resection and location. The allowed treatment modalities include conformal or intensity-modulated radiation therapy using photons or proton therapy using all available methods.

5.2 Treatment Planning and Specifics

The guidelines for this study were based on the experience treating patients with ependymoma at St. Jude Children's Research Hospital. This includes patients treated with radiation therapy at the time of initial diagnosis as well as recurrence after prior focal irradiation. Patients with local failure will be treated with surgery and a second course of focal irradiation. The total dose for the second course of irradiation for most cases will be 54Gy. The total dose may be attenuated for patients with prior history of significant treatment-related complications or in the setting of significant dose heterogeneity or high-dose treatment volumes. Patients with metastatic failure will be treated with metastasectomy and craniospinal irradiation. Craniospinal irradiation (36-39.6Gy) will include focal boost treatment of primary and metastatic sites (50.4-59.4Gy) depending on location, extent of resection and target volume. Patients with combined local failure will undergo metastasectomy, primary site resection and craniospinal irradiation.

Targeting the primary site for retreatment follows the principle of minimizing dose to normal tissue, irradiating only the site of known recurrent disease and not irradiating the entirely of the tumor bed at the time of initial diagnosis. It is anticipated that some tissues will receive a combined dose 59.4Gy + 54Gy ~ 114Gy from the first and second courses of irradiation, respectively.

The prescribed dose for ependymoma has evolved to a standard of 59.4Gy when using a clinical target volume margin of 1cm for all children except those under the age of 18 months treated with gross-total resection. There are ample data demonstrating that these prescribed doses and target volumes are reasonable and safe. In the setting of recurrent disease and prior irradiation, the dose of 59.4Gy is appropriate for previously untreated brain and the limit for previously irradiated tissue will be 54Gy. The neuraxis dose for metastatic ependymoma has been chosen to achieve the highest level of disease control; however, there may be instances when portions of the neuraxis will receive less than 36Gy owing to concerns about potential risks.

The CSI component of treatment is planned and administered in a relatively conventional manner; however, limited volume irradiation of the primary site or metastatic sites after CSI is amenable to a spectrum of conformal planning and delivery techniques. The guidelines for this study are generalized to provide consistency in the targeting, dosimetry and reporting.

Investigator discretion will be used in various minor aspects of treatment including the total dose prescribed to the previously irradiated cervical spinal cord and brainstem, the total neuraxis dose, total spinal and intracranial dose for metastatic sites, and total primary site dose.

5.3 Indications for Radiation Therapy

Patients enrolled on this protocol will receive radiation therapy after documented evidence of tumor progression or recurrence. In most cases, surgery will be performed for diagnostic and therapeutic purposes prior to irradiation. The goal of surgery is to achieve gross total resection of all imaging visible residual tumor.

5.4 Timing

The general goal is to initiate radiation therapy within 12 weeks of last surgery performed at the time of recurrence; however, there is no required time interval from the time of surgery to the initiation of radiation therapy.

There are no contraindications to radiation therapy; however, patients taking phenytoin should be weaned and/or switched to a different anticonvulsant as soon as possible.

5.5 Emergency Irradiation

Urgent irradiation is not envisioned under any circumstance.

Equipment and Methods of Delivery and Verification: all photon and proton therapy modalities will be allowed on this protocol including all energy of photon and proton beams. Photon treatment may be indicated when proton systems are not available.

5.6 Treatment Planning

CT (volumetric) based planning is required to optimize dose to the neuraxis or target volume(s) while protecting normal tissues. Organs at risk within the irradiated volume should be contoured including those required. A dose-volume histogram (DVH) is necessary to determine target coverage and evaluate dose to normal tissues. CT section thickness should be < 2-3mm when planning for treatment of focal targets in the brain and < 5mm for craniospinal irradiation.

5.6.1 Treatment Planning

CT (volumetric) based planning is required to optimize dose to the target while protecting normal tissues. Organs at risk within and external to the irradiated volume should be contoured. A DVH is necessary to assess target coverage and evaluate dose to normal tissues. Three-dimensional imaging data will be the basis for treatment planning and will be used to define target volumes and organs at risk. The size, shape and location of the target volume and its relationship to the surrounding anatomy will be incorporated into the decision regarding the use of the specific planning method and the goals of treatment which include target volume coverage, normal tissue sparing, feasibility of delivery and the potential for verification. Target coverage and dose to critical structures will be evaluated by examining isodose distributions and dose-volume histograms for the target volumes and normal tissue structures. Based on these evaluations, the optimal plan that maximizes conformity of treatment and minimizes dose to normal tissues will be selected. The homogeneity of dose will be optimized across the targeted volumes.

5.6.2 CT Data

At the outset of this protocol, CT data will be obtained in the treatment position as the fundamental data set to which MR data will be registered for treatment planning and measurements of brain shift, target volume change and patient's positioning. The fundamental data set will include the volume from the vertex to the base of the skull and will hopefully encompass all tissues down to the level of the sternal notch. Each slice thickness will be approximately < 2mm throughout the volume. Intravenous contrast may be used unless it is contraindicated or deemed unnecessary by the treating radiation oncologist. The use of proton therapy necessitates a non-contrast CT in addition to a contrast-enhanced CT when acquired.

5.6.3 MR Data

MR data will be registered to CT data for planning and evaluation. MR data includes imaging obtained pre and post-operatively and studies performed as part of the planning process. Diagnostic imaging MR data (DIMR) will include 2- and/or 3-dimensionally acquired T1-weighted pre- and post-contrast imaging, T2-weighted imaging and post-contrast FLAIR sequences to identify tumor. Radiation oncology MR data (ROMR) will include imaging studies performed for planning purposes and during treatment to monitor for changes in target and normal tissue volumes and patient positioning.

5.6.4 Immobilization and Simulation

Patients will be immobilized according to their level of cooperation, clinical condition and the suitability of available devices relative to their tumor location and the goals of treatment. Daily general anesthesia will be used when required to achieve satisfactory immobilization and localization. At the outset of this

protocol, supine-position immobilization devices will be used. Fiducial markers may be placed prior to therapy when requested.

5.6.5 Verification Simulation

After treatment planning, the patient may need to be repositioned at the treatment isocenter (as defined by the treatment plan) for verification. This may take place in the simulator (CT or MR) or using the verification imaging systems associated with the treatment device.

5.6.6 Verification of Spatial Positioning

Portal and volumetric mV or kV imaging are interchangeably used to verify patient position.

5.7 Target Volumes

General Comments International Commission on Radiation Units and Measurements (ICRU) [216-218] Reports 50, 62 and 78 define prescription methods and nomenclature that will be utilized for this study. Although the MRI obtained immediately prior to radiation therapy should be used for treatment planning, the target volumes for this study will be determined by the collective information that delineates the extent of disease before and after surgical resection of recurrent tumor. Most patients with ependymoma require a combination of pre- and post-operative MR sequences to delineate the extent of disease. MR pre- and post-gadolinium contrast T1, T2, and FLAIR sequences should be reviewed. The sequence that best defines the extent of residual disease and post-operative tumor bed should be used to determine the GTV and registered to the treatment planning CT. Registration of the PET studies may also be useful. The GTV, CTV and PTV and normal tissues must be outlined on all axial imaging slices on which the structures are visible.

5.7.1 Targeting for patients with local recurrence

Primary Site Irradiation

The patient with recurrent disease at the primary site and no evidence of metastasis will receive focal irradiation of the primary site using the targeting guidelines provided below. Exceptions will include patients with tumors demonstrating the presence of 1q gain at any point in their treatment history. They will be given the option of craniospinal irradiation and will follow targeting guidelines similar to those who have metastatic disease.

5.7.2 Targeting for patients with metastatic disease

Craniospinal Irradiation (CSI): The CSI volume includes the entire subarachnoid volume with special attention to identification and inclusion of the cribriform plate and temporal fossae intracranially; the full width of the spinal subarachnoid space intraspinally and the inferior aspect of the thecal sac. CSI will be reserved for patients with evidence of neuraxis dissemination based on evaluation of CSF cytology or imaging of the brain and spine and will be given according to the guidelines provided below.

Primary Site Irradiation: Patients with metastatic disease may also have evidence of primary site failure and will receive supplemental irradiation to the primary site immediately following craniospinal irradiation. Targeting guidelines for the treatment of the primary site in this setting will follow the guidelines used for primary site irradiation in the absence of metastatic disease.

Metastatic Site Irradiation: Treatment of metastatic disease requires investigator discretion. All resected lesions and overt metastatic disease >0.3cm in maximal thickness should receive supplemental irradiation in addition to CSI when practical. Smaller lesions may also be treated at the discretion of the treating physician. This will include lesions in the brain and spine and using the guidelines outlined below.

5.8 Definitions for GTV, CTV and PTV

5.8.1 Gross Tumor Volume

Gross tumor volume (GTV) is based on the post-operative MR examination and includes gross residual tumor and the tumor bed at the primary site. In defining the GTV, the investigator should consider the pre-operative imaging examination that defined the extent of recurrent tumor and the tissues involved anatomically. The GTV in most cases will be a contracted or collapsed tumor bed. Tissue defects resulting from surgical approaches will not be included as part of the GTV when not previously involved by tumor. Investigators should register the pre-operative MR imaging sequence that demonstrated tumor and contour the structure to be identified as GTV_PREOP to assist in the delineation and evaluation of the GTV. In the setting of gross-total resection, the post-contrast T1-weighted MR sequence is generally the most useful. In the setting of non-enhancing residual disease, T2-weighted imaging may be required. The GTV will take into account changes in brain anatomy resulting from tumor resection or CSF shunting.

- GTV is the volume of tissue containing the highest concentration of tumor cells.
- GTV includes the post-operative tumor bed which is the edge of the resection cavity.
- GTV includes residual disease defined by post-operative neuroimaging.

- The surgical corridor should not be included in the delineation of the GTV unless suspected to contain tumor.
- When there is discrepancy between imaging studies or intra-operative findings, the larger volume will define GTV.

5.8.2 Clinical Target Volume

Clinical target volume (CTV) includes the GTV with an added margin that is meant to treat subclinical microscopic disease and is anatomically confined (i.e., the CTV is limited to the confines of the bony anatomy, dura, falx and tentorium where applicable or extends up to but not beyond neuroanatomic structures through which tumor extension or invasion is certain not to have occurred); the CTV margin should not exceed 0.5cm and should generally include 0.3cm of normal tissue. When the GTV approaches the boundary of an anatomic compartment, the CTV will extend up to and include the boundary. The CTV margin chosen for this study requires treatment planning MR and/or diagnostic MR imaging data with image section thickness ≤ 0.5cm.

- CTV is defined as the volume of tissue containing subclinical microscopic disease
- CTV for this protocol is the GTV with an anatomically confined margin of ≤ 0.5cm
- CTV should be tailored at tissue interfaces where invasion/infiltration is not likely
- CTV may be manually moved inward to the inner-table of the bony calvarium
- CTV may be limited to the brainstem surface which is ≤ 0.2-0.3cm depth of the brainstem contour.

5.8.3 Planning Target Volume

Planning target volume (PTV) is a concept associated with photon therapy includes a margin which is added to the CTV in 3-dimensions to create the PTV. It is geometric and not anatomically defined. The PTV has two components, the internal margin (IM) and the set-up margin (SM). The IM is meant to compensate for all movements and variations in size and shape of the tissues contained within the CTV. The SM is meant to account for set-up, mechanical and dosimetric uncertainties related to daily patient positioning, treatment equipment and software. For this study, the PTV margin should be 0.2-0.3cm. The use of a PTV margin of 0.2-0.3cm requires image-guided radiation therapy methods are used on a daily basis or alternatively a fixation system or verification system with similar performance. Given that the CTV is generally confined to the intracranial space, the PTV may extend into or beyond bone but is unlikely to extend beyond the surface of the patient. The PTV margin chosen by the treating investigator requires treatment planning MR and/or diagnostic MR imaging data with imaging section thickness ≤ the chosen PTV margin. In summary, the PTV will include the

CTV plus a geometric margin of 0.2-0.3cm in all dimensions. The PTV may extend beyond bone margins and the skin surface.

Craniospinal Irradiation (CSI): The CSI volume includes the entire subarachnoid volume with special attention to identification and inclusion of the cribriform plate and temporal fossae; the full width of the spinal subarachnoid space and the inferior aspect of the thecal sac.

Craniospinal Irradiation-CT Planning: CT studies obtained uniquely for the CSI planning process are allowed and may also serve as the basis for planning boost treatment. CT studies will be performed whenever possible and the information used for craniocaudal intensity modulation. For the cranial component of treatment, the external contours of the skull and neck are viewed in the AP direction and points are chosen to divide the cranial field into 2-4 fields to achieve a field-within-a-field plan and lateral homogeneity over the craniocervical junction. For the spinal component of treatment, the spinal cord and canal are contoured and viewed laterally and points are chosen to divide the spinal field into 4-6 fields to achieve field-within-a-field plan and antero-posterior homogeneity over the spinal cord and thecal sac. The following parameters are suggested: volume - cranial vertex to perineum; section thickness < 5mm; image matrix - 512^2. The administration of IV contrast is not required.

Patients may have one or more metastatic lesions. These lesions may or may not be surgically removed. The nomenclature for the targeted volumes will follow those used for primary site irradiation with additional descriptors mean to assist in the evaluation of the case after the completion of treatment. For example, MGTV1_intracranial or MGTV1_right_lateral ventricle and subsequent modifications for CTV and PTV will be helpful.

Relevant to proton therapy, the PTV may be used to select the appropriate beam size and beam arrangements to achieve lateral coverage of the targeted volume and to minimize heterogeneity. The PTV will not be used to determine the distal range for the individual proton beams but will be used to report dose according to ICRU Report-78. The proton distal target margin will be determined per beam using the guidelines noted in this protocol.

5.9 Target Dose

5.9.1 Dose Definition

Photon dose is to be specified in centigray (cGy)-to-muscle. For proton therapy, the absorbed dose is specified in CGE, which is the same as ICRU 78 DRBE [218] using a standard RBE of 1.10 with respect to water. The units of Gy and CGE will be interchangeable with reference to prescription dose, normal tissue constraints, etc.

5.9.2 Prescribed dose and fractionation

The patient should be treated with one fraction per day. All fields should be treated each day in photon treatments. Simultaneous integrated boost is not allowed.

Table Prescribed Doses and Fractionation

Total Dose by Site	Target Volume	Dose/fraction	Number of Fractions
Neuraxis 3600-3960CcGE/cGy	CTV_{CSI}/PTV_{CSI}	180CcGE/cGy	20-22
Primary Site 5040-5400cGy	CTV_{PS}/PTV_{PS}	180CcGE/cGy	10-30
Metastases 5040-5940cGy	CTV_{X}/PTV_{X}	180CcGE/cGy	5-13

The total dose to the target volume CTV (proton) or PTV (photon) prescription isodose surface will be 5400CcGE/cGy administered in 30 fractions of 180CcGE/cGy. The patient should be treated with one fraction per day. All fields should be treated each day in photon treatments. Exceptions will include unanticipated changes in patient's clinical condition, logistical considerations owing to holidays, weather, equipment failure and the need to complete the course of treatment in the least number of elapsed days. Two treatments in one calendar day will be discouraged. We will consider a single fraction reduction in the dose regimen for cases where significant dose heterogeneity are encountered. Investigator discretion may be used to alter the dose per fraction 150-200CcGE/cGy per day when indicated and requires PI approval. The total dose may be attenuated – 3420CcGE/cGy instead of 3600CcGE/cGy CSI or 5040CcGE/cGy instead of 5400CcGE/cGy primary site - for patients with prior history of significant treatment-related complications or in the setting of significant dose heterogeneity or high-dose treatment volumes. We will also consider alterating the craniospinal dose when there are concerns about excessive risks regarding treatment-related complications,

5.9.3 Dose Uniformity

Photon Therapy Goals: At least 95% of the protocol-specified dose should encompass 100% of the PTV and no more than 10% of PTV should receive greater than 110% of the protocol dose as evaluated by DVH. The 100% isodose should be equal to the protocol specified dose. All methods of generating more uniform dose distributions are encouraged. For craniospinal treatments, the dose will be measured at the midplane of the cranial volume and at the posterior border of the vertebral body the spinal field(s) including the dose at the central ray. Effort should be made to minimize inhomogeneity at the craniocervical junction when possible and the gradient of dose across the spinal cord.

Proton Therapy Goals: At least 95% of the protocol-specified dose should encompass 100% of the CTV and no more than 10% of CTV should receive greater than 110% of the protocol dose as evaluated by DVH. The 100% isodose should be equal to the protocol specified dose. The PTV may be used to select the appropriate beam size and beam arrangements to achieve lateral coverage of the targeted volume and to minimize heterogeneity. The lateral margin for proton therapy should be approximately 3mm. The PTV will not be used to determine the distal range for the individual proton beams. The proton distal target margin will be determined per beam based on the distal aspect of the CTV and additional margin(s) meant to account for range uncertainty and the SM and IM components of the PTV which are understood for this group of patients and which may affect the proton distal range.‡

Proton Distal Target Margin† = CTV + Range Uncertainty + Set-up Margin + Internal Margin

- CTV = the distal aspect of the CTV
- Range Uncertainty = 3% of the water-equivalent range of the CTV at max depth
    - ≥ 1mm
- Set-up Margin = set-up, mechanical, dosimetric and registration uncertainties
    - Protons are relatively unaffected by set-up uncertainty in axis of beam. Setup errors for brain in general do not have an impact on range per se.
    - Uncertainty in hardware and software – no assigned value available Uncertainty in accuracy of image registration
        - ≥ 1mm
- Internal margin = compensates for all variations in site, size and shape of the tissues contained in or adjacent to the CTV. We assume no internal organ motion.
    - ≥ 1mm

†The proton distal range may be adjusted at the discretion of the treating radiation oncologist based on normal tissue dose concerns.
‡The uncertainty of distal margin has been estimated to be as large as 3-4mm.

For the rare case treated using photon therapy due to equipment failure, at least 95% of the protocol-specified dose should encompass 100% of the PTV and no more than 10% of PTV should receive greater than 110% of the protocol dose as evaluated by DVH. The 100% isodose should be equal to the protocol specified dose. Methods of generating more uniform dose distributions are encouraged.

When pencil beam scanning techniques are used with scenario-based optimization (e.g., robust optimization), the plan may be optimized for 100% of the CTV to receive 95% of the protocol-specified dose. The protocol-defined PTV may be reviewed to confirm coverage.

5.9.4 Tissue Heterogeneity

Calculations must take into account tissue heterogeneity and should be performed with CT-based treatment planning to generate dose distributions and treatment calculations from CT densities.

5.9.5 Interruptions, Delays and Dose Modifications

There will be no planned rests or breaks from treatment, and once radiation therapy has been initiated, treatment will not be interrupted except for any life threatening infection or severe hematological toxicity defined as ANC < 300/μL or platelets less than 20,000/μL during the course of treatment. Blood product support is not required. The reason for any interruptions greater than 3 treatment days should be recorded in the patient treatment chart. There should be no modifications in dose fractionation due to age or field size.

Sequencing Contingencies: CSI will generally be given first, followed by boost therapy. Boost therapy may be initiated prior to craniospinal irradiation if required by the medical condition. In all cases when CSI is deferred, it should be initiated as soon as medically feasible, before the completion of boost therapy if feasible. If CSI is interrupted for >4 days for medical reasons, the boost should be started until CSI can be resumed.

5.10 Treatment Technique

5.10.1 Beam Configuration

Every attempt should be made to minimize dose to organs at risk without compromising coverage of the target volume. Three-dimensional conformal or intensity-modulated radiation therapy using photons or protons are required to minimize dose to normal tissues.

5.10.2 Field Shaping

Photon field shaping will be done with multileaf collimation.

5.10.3 Patient positioning

Reproducible setups are critical and the use of immobilization devices is strongly encouraged. The patient may be treated in any appropriate, stable position. Consideration should be given to implications for inter and intra-fraction motion when using non-standard position approaches.

5.10.4 Immobilization devices

Standard immobilization devices for the torso, extremities or head and neck are to be used. For IMRT delivery approaches, the methods used for localization and immobilization of both patient and tumor are critical. The imaging studies should

provide a clear assessment of the target volume with the patient in the treatment position.

5.10.5 Special considerations

Anesthesia or sedation may be required in certain patients, such as very young patients, to prevent movement during simulation and daily treatments.

5.10.6 Motion Management and Margins to Account for Target Volume

Considering motion of normal tissues and target volumes is important. The internal target volume (ITV) is defined as the CTV surrounded by the IM component of the PTV and is meant to account for potential motion or changes in the CTV. The planning organ at risk volume (PRV) includes the corresponding organ at risk (OAR) volume surrounded by a margin to compensate for motion or physiologic change in the OAR. If adequate clinical data do not exist to define the IM component of the PTV or the PRV margin, the following suggestions are provided:

- Margin matching the PTV margin may be added to OAR to form the PRV.
- Brain tumors susceptible to cyst expansion should be monitored closely.
- Any change in clinical condition or anatomy related to hydrocephalus, VP shunt placement, subdural fluid, pseudomeningocele or steroid use should be monitored carefully and with repeat imaging when indicated.
- Portal and volumetric imaging may be performed at the completion of individual treatment sessions to assess the individual patient's set-up uncertainty and prescribe the appropriate margins to account for set-up uncertainty.

5.10.7 Radiosurgery

Under certain circumstances patients will be treated with primary radiosurgery. These patients will be treated with tumor ablative doses according to institutional and cooperative group guidelines. Tolerances to normal tissue structure according to the same guidelines will also be observed.

Radiosurgery is a standardized procedure and will be considered for the primary or boost treatment of selected patients with residual primary or metastatic disease. This treatment may be carried out using the linear accelerator or Gamma Knife. Patients will undergo a CT or MR scan for stereotactic localization following the placement of a neurosurgical head frame. A dose in the range of 1000-1500cGy will be delivered to the patients receiving boost treatment and generally 1500-2100cGy to patients receiving primary radiosurgery. The dose selected depends on the size of the target volume. The treatment will be single fraction and the dose will be described to the isodose line encompassing the target volume. In general, the target volume will be encompassed by the 80-90% isodose surface for linac-

based radiosurgery and the 50-60% isodose surface for Gamma Knife. The brainstem dose will be less than 1200cGy and the dose to the chiasm will be limited to 800cGy.

5.11 Treatment Planning Procedures

Craniospinal Irradiation: Patients may be simulated and treated in the prone or supine position using customized immobilization devices that allow for verification of cranial and spinal field junctions. Treatment will be given using standard techniques, encompassing the entire subarachnoid volume (both brain and spine). The technique should assure coverage at the cribriform plate and temporal fossae intracranially; the full width of the spinal subarachnoid space (dosimetrically to include the medial aspect of the neural foramina) down to the bottom of the thecal space (as indicated by sagittal spinal MR).

Infratentorial Irradiation: Consideration should be given to minimizing dose to the brainstem and spinal cord.

Supratentorial Irradiation: Consideration should be given to minimize dose to the optic apparatus including the eyes, nerves and chiasm.

Metastatic Site Irradiation: MR visible intracranial metastatic disease should be treated concurrently with the primary site and when feasible joined to the primary site volume. The decision to treat separate or combined primary and metastatic boost volumes should be based on limiting normal tissue irradiation. Spinal metastatic disease should be treated concurrently with the primary site treatment.

5.12 Organs at Risk

The organs at risk guidelines in this section are recommendations. If the recommended doses to the organs at risk are exceeded because of target volume coverage requirements or other conditions, an explanation should be included in the quality assurance documentation. Note these guidelines are for the current treatment protocol and do not represent cumulative target doses.

5.12.1 Cochleae

- D50% < 3500cGy – Goal (single cochlea)
- D50% < 2000cGy – Preferred (single cochlea)
- Comment – There is no dose limit for the cochleae.
- Structure definition - Each cochlea will be contoured on the treatment planning CT as a circular structure within the petrous portion of the temporal bone. The contour should appear on at least two successive CT images.

5.12.2 Optic Globes

- D50% < 1000cGy and D10% < 3500cGy – Goal

- D50% < 2000cGy and D10% < 5400cGy – Maximum
- Comment – Effort should be made to avoid direct treatment of the anterior chamber of the eye and minimize dose to the entire eye without compromising target volume coverage. In the event that the recommended maximum dose constraints provided in this section would be exceeded, the treating radiation oncologist may use their discretion to reduce target volume coverage.
- Structure definition - Each eye should be separately contoured on the treatment planning CT or MR as a circular structure from the most superior to inferior aspect.

5.12.3 Optic Nerves and Chiasm

- D50% < 5400cGy and D10% < 5600cGy – Goal
- D50% < 5600cGy and D10% < 5800cGy – Maximum
- Comment – Effort should be made to avoid direct treatment of the optic nerves and chiasm without compromising target volume coverage. In the event that the recommended maximum dose constraints provided in this section would be exceeded, the treating radiation oncologist may use their discretion to reduce target volume coverage.
- Structure definition – The optic nerve may be contoured on CT or MR. The contour should appear on at least two successive CT or MR images.

5.12.4 Spinal Cord

- D50% < 2600cGy and D10% < 5700cGy - Goal
- D50% < 5000cGy and D10% < 5900cGy – Maximum
- Comment – Effort should be made to minimize dose to the spinal cord without compromising target volume coverage. In the event that the recommended maximum dose constraints provided in this section would be exceeded, the treating radiation oncologist may use their discretion to reduce target volume coverage.
- Structure Definition - For the purposes of this study, the upper aspect of the spinal cord begins at the inferior border of the foramen magnum and should be contoured on the treatment planning CT. For purposes of comparison and consistency with dose volume data, the spinal cord should be contoured on a number of images to be determined by the image section thickness (CT section thickness, n=number of images; 2mm, n=30; 2.5mm, n=24; 3mm, n=20). Using these guidelines, only the superior-most 6cm of anatomic spinal cord is contoured.

5.12.5 Brainstem

- D50% < 6100cGy and D10% < 6300cGy - Goal
- D50% < 6200cGy and D10% < 6400cGy – Maximum

- Comment – Effort should be made to minimize dose to the brainstem without compromising target volume coverage. In the event that the recommended maximum dose constraints provided in this section would be exceeded, the treating radiation oncologist may use their discretion to reduce target volume coverage.
- Structure Definition - The brainstem may be contoured on the treatment planning CT or MR and will include the midbrain, pons and medulla. The cranial extent will be inferior to the IIIrd ventricle and optic tracts. The caudal extent will end at the foramen Magnum. A brainstem core representing tissue ≥ 3mm depth from the brainstem surface may be contoured when indicated.

5.13 Dose Calculations and Reporting

5.13.1 Prescribed Dose

The dose should be prescribed to an isodose surface that encompasses the CTV (proton) or PTV (photon) and allows the dose uniformity requirements to be satisfied.

5.13.2 Normal Tissue Dosimetry

The dose to the critical organs indicated should be calculated whenever they are directly included in a radiation field. A DVH must be submitted for a category of tissue called “unspecified tissue,” which is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure. A DVH for “Body” shall be submitted to enable calculation of the required volumes. “Body” is defined as the outer contour of the patient on the treatment planning CT data set.

Required DVH data regardless of primary treatment site

Required DVH
Optic Chiasm
Brainstem
Spinal Cord
Right Cochlea
Left Cochlea
Body

Unspecified Tissue

Treated Volume, Irradiated Volume and Conformity Index (CI)
The treated volume (TV) is the tissue volume that receives therapeutic dose. For the purpose of this protocol this would include the prescribed total dose of 54-59.4Gy and 95% of the prescribed dose. This information may be used by the investigators, along with the absolute volume of the PTV, to calculate the conformity indexes (CI) $CI_{100\%}$ and $CI_{95\%}$, respectively. The irradiated volume (IV) is the tissue volume that receives a dose that is considered significant in relation to normal tissue tolerance. The descriptive statistics for these and other tissue volumes maybe used for correlation with unusual side effects or to develop practical guidelines for future brain tumor protocols.

Required Volumetric Information

• Required Volumes
TV95%=V56.4 Gy
TV100%=V59.4Gy
IV35=V35Gy
IV45=V45Gy
IV54=V54Gy
PTV
CTV
GTV
Entire Brain
Unspecified Tissue

5.14 Patterns of Failure Evaluation

The patterns of failure for patients with ependymoma may be described as local, distant or a combination of local and distant based on imaging evaluation of the neuraxis. Local failure is defined as progression or recurrence of tumor at the primary site of disease. Distant failure is defined as the progression or recurrence of tumor at a location other than the primary site. Distant failure most often occurs in the subarachnoid space and may occur at any point within the neuraxis. Although rare, extra-CNS metastasis represents distant failure. Combined local and distant failure is defined when evaluation of the entire neuraxis reveals synchronous local and distant failure.

The present study involves treatment of the primary site only, neuraxis with or without supplemental primary and metastatic site irradiation. Because the prescription dose will be confined to a limited volume encompassing the tumor and/or tumor bed, it is possible that the volume that receives the prescription dose will not subtend the entire area at risk and that the rate of failure for patients treated using the guidelines will be driven by targeting. Determining the patterns of failure will require an assessment of tumor recurrence with respect to targeting and dosimetry. Failure may be described as in-field, marginal or out-of-field when focal irradiation techniques are used. Out-of-field failure is recurrence that occurs entirely outside of the CTV and is synonymous with distant failure. In-field failure is recurrence that originated entirely within the volume that was targeted to receive the prescription dose (CTV). Marginal failure is recurrence originating on the margin of the volume targeted to receive the prescription dose (CTV) and may be described in terms of location or the dose received.

There is no universally accepted analytical method to assess pattern of failure and to determine whether failure is in-field, marginal or out-of-field. For this study, the pattern of failure will be assessed qualitatively and quantitatively by registering MR data obtained at the time of failure to the dosimetry from the original treatment plan. Failures will be determined qualitatively to be “in-field” when the recurrence appears to have originated from within and remains confined to the CTV, “marginal” when a portion of the recurrence is within the CTV but the majority of the recurrence is outside of the CTV, “distant” when the recurrence does not involve the CTV. Recurrences will be quantitatively categorized as in-field, marginal, or out-of-field based on the proportion of the recurrence that received at least 95% of the prescription dose. This requires contouring of the recurrence and computation of the dose-volume histogram. Marginal failure occurs when between 20 and 80% of the recurrence volume receives more than 95% of the prescription dose, thus, in-field failure occurs when more than 80% of the recurrence volume receives more than 95% of the prescription dose and out-of-field failure occurs when less than 20% of the volume received more than 95% of the prescription dose. Any method has limitations; however, since the point of origin for tumor recurrence cannot be ascertained with absolute certainty and does not explicitly determine marginal failure. Because of this finding, we are not certain of the best method to define the patterns of failure at this time.

5.15 Management of Radiation Necrosis

When early signs of progressive parenchymal changes are present on imaging we will consider referral for hyperbaric oxygen therapy (HBOT). HBOT may be recommended when progressive parenchymal changes are associated with mild to moderate symptoms. Steroid therapy, most often dexamethasone, may be initiated and tapered according to symptoms. When the dose of dexamethasone has been tapered to approximately 0.5mg daily, a taper of hydrocortisone will be initiated at approximately 25mg daily administered in divided doses. Dexamethasone will be discontinued within 2-3 days of the initiation of the hydrocortisone. Patients

are not required to remain on steroid therapy during HBOT. In the setting of severe symptoms, medical oncology may be consulted to consider other measures including the use of bevacizumab.

5.16 PET for Dose Verification of Proton Therapy

The number of PET activation studies will equal the number of proton treatment beams, which is estimated to be 3 for the majority of cases. On the day of the PET evaluation, the patient will be treated with a single beam corresponding to the activation beam under study. A separate plan may be developed to ensure the prescription dose to the target using a single beam on that day and that a critical normal tissue volume will not be compromised by the end of range uncertainty in RBE. The beam on time and duration for each of the single field treatment fractions will be recorded. The duration of the single beam fraction is estimated to be 10 to 15 minutes shorter than the conventional fraction. At the end of the single beam fraction, the patient will be transported to the PET-CT; estimated time required is 10 minutes. For PET attenuation correction and anatomic localization purposes, a CT of the cranium will be obtained; estimated time required is 5 minutes. The PET activation study will then be acquired for 30 minutes; the start time will be recorded. Based on the treatment plan, a Monte Carlo simulation of the positron activation locations and intensities will be created. The predicted image and acquired image will be compared and analyzed.

Alternatively, the patient may be treated with one beam, have the PET activation study and then complete the treatment with the remaining beams.

6.0 REQUIRED EVALUATIONS, TESTS AND OBSERVATIONS

Instructions regarding the logistics of baseline evaluations

Surgery→enrollment→no surgery→ radiation therapy

If surgery was performed prior to enrollment and the patient does not require additional surgical intervention, similar to the preceding section, they should be enrolled on protocol and undergo baseline evaluation prior to radiation therapy.

Surgery→enrollment→surgery→ radiation therapy

Regardless of prior surgical history, patient who will undergo additional surgery should be enrolled on protocol and undergo baseline evaluation prior to surgery. If they are unable to complete the required baseline evaluations prior to surgery, partial evaluation will be accepted and the remaining baseline evaluations should be completed after surgery (i.e., partial evaluations prior to and following surgical intervention will be accepted). Investigators should consider repeating aspects of

the baseline evaluation (e.g., diagnostic imaging, neurological examination, ophthalmology, etc.) that may be altered by surgery.

Instructions Regarding the Logistics of Follow-up Evaluations

It is the intent of the investigators to perform follow-up evaluations to meet the primary objectives and research the exploratory aims (Table 6.0.2). Performance will be regularly monitored according to institutional guidelines and by the principal investigator. Principal Investigator will closely monitor compliance and, when necessary, will establish contact with primary care providers and engage home health nursing, to ensure completion of protocol-specified evaluations. It is a requirement that all patients enrolled at St. Jude undergo all evaluations. Patients enrolled at collaborative sites may have evaluation requirements tailored to the availability of local resources.

Sponsorship

In the event that patients are enrolled at collaborative sites, the costs associated with research, treatment, follow-up and routine medical care will be the responsibility of the enrolling institution, patient and their family.

Protocol Performance

Despite the intent to adhere as closely as possible to the guidelines of this study, it is understood that unforeseeable circumstances may dictate postponement, cancellation or minor deviation in protocol guidelines because of intercurrent illness, logistical problems, and the absence of care providers or investigators, shortages in time and materials and lack of funding. Exceptions to the evaluation scheme will be made at the discretion of the Principal Investigator when clinical or logistical considerations preclude protocol-timely evaluation.

Research Data

The exploratory data derived from this study will be collected, analyzed and reported while the study is ongoing and with the approval of the Principal Investigator. The analyzed data will be reported and presented at institutional and scientific meetings and at invited presentations with the approval of the Principal Investigator. Use of the protocol data and publication of analyzed data is anticipated prior to completion of the study in the form of ongoing or preliminary reports and will be done only with approval of the Principal Investigator.

6.1 Physical Examination

Physical examination will be performed before, during and after radiation therapy. The patient height, weight and body-mass index will be recorded and converted to percentiles based on age and gender.

6.2 Neurology

At baseline and with each visit the pediMIDAS form will be completed. Grade 3-5 neurological complications will be reported using the NCI Common Toxicity Criteria v4.0.

6.3 Ophthalmology

At the specified time points and when clinically indicated, patients will be assessed in the ophthalmology clinic. The ophthalmologic examination may consist of an assessment of external signs of treatment sequelae, visual acuity, current correction, color vision, intraocular pressure, mobility, refraction and visual field. The ophthalmology data sheet will no longer be collected in paper version. This data will be extracted directly from the patient's medical record clinical documentation and entered directly into the trial database.

6.4 Audiology

Schedule: Patients will be referred for audiological testing prior to radiation therapy and annually dated from the start of RT. More frequent evaluations may be considered by the treating physician or audiologist based on results of prior evaluations and the potential risk for hearing loss.

Tests and Outcome Measurements: At each evaluation tympanometry will be performed to assess integrity of the conductive mechanism, distortion product otoacoustic emissions will be assessed to determine cochlear outer hair cell function, a pure tone audiogram will be obtained to assess peripheral hearing sensitivity, and speech-in-noise testing will be administered to assess performance in background noise and to screen for auditory processing disorder in children. Each audiogram will include air conduction thresholds at 250, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hertz measured in dB HL. Ultra-high frequency thresholds will be obtained at 9000, 10000, 11200, 12500, 14000, and 16000 Hertz in patients older than 5 years. Bone conduction thresholds will be obtained as needed to rule out a conductive component to the hearing impairment. Hearing will be categorized as normal if all thresholds are within the 0-20 dB HL range. If a deficit is present, hearing impairment will be categorized by the numerical dB HL values. Speech-in-noise testing will be administered to patients older than 5 years. The QuickSIN speech-in-noise test [219] will be administered to patients older than 14 years and the BKB-SIN speech-in-noise test [220] will be used for patients 5-14 years and for adults whom the QuickSIN test is too difficult.

An auditory brainstem response (ABR) evaluation may be substituted for patients who are unable to respond to conventional audiometric testing techniques.

Every audiogram or ABR evaluation will be assigned a grade based on the Chang and SIOP Ototoxicity Grading Scales.

Ototoxicity Grading Scales*

Chang		SIOP	
Grade 0	≤ 20 dB at 1, 2, and 4 kHz	Grade 0	≤20 dB HL at all frequencies
Grade 1a Grade 1b	≥ 40 dB at any freq 6 to 12 kHz > 20 and < 40 dB at 4kHz	Grade 1	>20 dB HL (i.e., 25 dB HL or greater) SNHL above 4000 Hz (i.e., 6 or 8 kHz)
Grade 2a Grade 2b	≥ 40 dB at 4 kHz and above > 20 and < 40 dB at any freq below 4kHz	Grade 2	>20 dB HL SNHL at 4000 Hz and above
Grade 3	≥ 40 dB at 2 or 3 kHz & above	Grade 3	>20 dB HL SNHL at 2000 Hz or 3000 Hz and above
Grade 4	≥ 40 dB at 1 kHz and above	Grade 4	>40 dB HL (i.e., 45 dB HL or more) SNHL at 2000 Hz and above

*Sensorineural Hearing Threshold (dB HL) bone conduction or air conduction with normal tympanogram

6.5 Endocrinology

To establish a baseline, patients will be evaluated for evidence of endocrinopathy and abnormal growth and development. They will be seen by the endocrine service at baseline and then at least once annually to document their developmental exam and to perform auxological measurements.

When necessary, the baseline and follow-up developmental exam and auxological measurements may be performed by a trained co-investigator.

Endocrine Imaging: Baseline evaluation will include 1) a plain film postero-anterior X-ray of the left hand and wrist for bone age; 2) quantitative CT; and 3) DXA scan for bone mineral density for participants ≥ 3 years of age. These examinations will be repeated when deemed necessary by the treating physicians.

Serum Screening Studies: Hypothalamic-pituitary axis function will be assessed with static assessments of fasting serum: thyrotropin (TSH), free and total thyroxine [212], reverse and total T_3, cortisol (obtained by 0800 hours), prolactin, insulin-like growth factor binding protein-1 (IGFBP-1, marker of insulin resistance) and insulin-like growth factor binding protein-3 (IGFBP-3), IGF-1, LH, FSH, insulin, 25(OH)D, serum Comprehensive Metabolic Panel (CMP) and complete blood count. These evaluations will be performed with each planned follow-up. These screening tests resemble those drawn for routine evaluation.

Understanding the pan-endocrine status is critical to interpretation of the GH data from the provocative testing.

Provocative Endocrine Testing: Patients will undergo evaluation for growth hormone and ACTH secretion abnormality using provocative tests of endocrine function. Recent steroid or growth hormone usage by the patient will be reviewed by the PI to determine when and if provocative endocrine testing shall be performed. GH provocative testing will be performed using arginine and carbidopa-levodopa. ACTH secretion will be tested using the 1 μg ACTH test. Similar evaluations will be repeated at 12 and 24 months after irradiation. The protocols used for provocative testing are identical to those used for patients in whom endocrinopathy is suspected. Exceptions to the endocrine testing procedures may be made at the discretion the treating physicians. Testing procedures may be omitted or modified: 1) because the patient is receiving replacement therapy; 2) when the provocative agent is unavailable; or 3) when the procedure is deemed inappropriate based on patient's clinical condition, 4) the intraday timing of the drug administration, or 5) phlebotomy is constrained by logistic problems.

6.6 Neuropsychological Testing

6.6.1 Overview of Neurocognitive Studies – Schedule

Patients will be referred for neurocognitive testing before radiation therapy and yearly through 5 years. All measures in the battery described below will be administered at yearly time points with the exception of the CVLT-C/CVLT-II, which will be administered only at baseline, 2 years post radiation therapy and 4 years post radiation therapy in order to minimize practice effects. We will not perform cognitive assessments on children less than 3 years of age, children for whom a language other than English is their primary language, or children with premorbid neurological/neurodevelopmental disorders (e.g., Down Syndrome, Autism).

6.6.2 Neurocognitive Testing

Children will be assessed at baseline (pre re-irradiation therapy and up to 4 months after the initiation of treatment) and annually for 5 years. An effort was made to select measures that could assess the widest study age range possible. Another primary goal was to select a battery that could be administered in a circumscribed period of time to reduce the time burden for children, their parents and the research team. The administration time for the test battery is estimated at 2-3 hours, dependent on the age of the child and the speed with which they can complete tasks. Therefore, the administration length of the current battery readily lies within the standard length of typical clinical and research batteries. All selected measures have age-specific norms from large, representative standardization samples. Measures also have appropriately demonstrated reliability and validity. Given the longitudinal study design, measures were

chosen with appropriate test-retest reliability and negligible practice effects for the proposed interval between testing time points. Tasks were chosen that balance the need to measure global outcomes typically assessed with respect to treatment interventions and most useful for educational planning (e.g., IQ and academic achievement) with specific areas of deficit most commonly reported in the brain tumor literature for children receiving radiation therapy (e.g., attention, processing speed and executive functions). See Table 1 for a listing of measures by cognitive domain.

Measure of Intellectual Function

Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) [221]: The WISC-IV is the fourth edition of the WISC and the most commonly used measure to assess intelligence in children 6-16:11 years of age. The Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) [222] will be administered to children 17:0 and older. We propose a shortened administration of 8 subtests that provides a prorated full-scale IQ score and also allows for the derivation of the Verbal Comprehension, Perceptual Reasoning, Working Memory and Processing Speed Indices (60 to 90 minutes). Children ages 3.0-5.11 will complete the age-appropriate subtests from the Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III) [223], which allows for the calculation of a Full-Scale IQ, Verbal IQ, Performance IQ, and a Processing Speed Index. (60-90 minutes)

Attention and Executive Function Measures

CogState [224]: CogState is a battery of computerized, semi-automated assessment measures (www.cogstate.com) that can be administered and proctored by examiners/research assistants with minimal training. All responses are recorded by the computer system including speed (reaction time) in milliseconds thus providing a reliable index of processing speed and psychomotor functioning that is highly relevant to this study population. Test batteries can be customized for research questions and study populations. The battery included here is composed of 5 tasks (Detection, Identification, One-Back, Continuous Paired Associate Learning, and Groton Maze) that assess processing speed, visual attention, working memory, visual learning and executive functioning. Age-based standard scores are computed for each task based on a normative sample. The battery is particularly well suited for longitudinal assessment as no practice effects have been identified when testing intervals are greater than one month [224, 225]. CogState has been used with typically developing children [226] as well as individuals diagnosed with attention deficit hyperactivity disorder (ADHD) [227], individual with concussions [228] and adult cancer patients [229].

The Detection, Identification and One-Back tasks are based on a playing-card paradigm. The Detection task is a simple reaction time task that measures psychomotor function. In this task, the child is required to press a "yes" button as

quickly as possible when the centrally located card turns face-up. The face-up card is always the same joker card and the task ends when 35 correct responses have been recorded (~2 minutes). The Identification Task is a choice reaction time task that measures visual attention. The presentation is similar to the Detection task but now the child responds "yes" if the face-up card is red and "no" if it is not red. The cards are red and black joker cards and the task ends after 30 correct trials (~2 minutes). The One-back task assesses attention and working memory. The child is instructed to respond "yes" if the face-up card is exactly the same as the immediately previous card or "no" if it is not the same as the previous card. The task ends after 30 correct trials (~3 minutes).

The Groton Maze learning test is a measure of the reasoning and problem solving aspects of executive function. In this task, participants are asked to move their way through a 10 x 10 grid of square tiles in which a 28-step pathway (with 11 turns) is hidden. Participants begin from a start location in the upper left corner of the grid and are instructed to find their way to the lower right corner of the grid. While moving through the hidden maze, participants find the tiles that are part of the hidden pathway by clicking on tiles. After each move is made, the computer indicates whether they are correct or incorrect. When the participant completes the pathway, he or she repeats this process (the same maze pathway) for four more trials. Total errors made while navigating the hidden maze across five trials is the outcome measure (~5 minutes). The Continuous Paired Associate Learning is discussed below under the memory measures.

Working Memory Index: The Digit Span and Letter-Number Sequencing tasks from the age-appropriate WISC-IV or WAIS-IV will be administered as measures of attention (Digit Span Forward) and working memory (Digit Span Backward; Letter-Number Sequencing). Forward span tasks are considered measures of attention and immediate recall, whereas backward span and sequencing tasks, with the additional requirement of reordering stimuli before responding, are regarded as measures of working memory.

Woodcock-Johnson Tests of Cognitive Abilities, Third Edition (WJ-III-COG) [230] Retrieval Fluency: The Retrieval Fluency subtest assesses verbal retrieval and fluency by requiring the child to name as many exemplars of a given category as they can in one minute. (3-5 minutes)

The Behavior Rating Inventory of Executive Function (BRIEF) [231]: The BRIEF is a parent questionnaire designed to assess behavioral manifestations of executive functioning. Executive functions include goal-directed behaviors, such as the ability to plan, organize, sustain performance, and change performance in response to feedback. (10-15 minutes)

Visual Spatial/Visual Motor Measures

The Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI) [232]: The VMI assesses visual-motor skills by requiring children to copy a series of increasingly complex shapes and figures as accurately as possible. The supplemental test of visual perception requires children to match identicalshapes that also become increasingly complex and the supplemental test of motor coordination requires children to draw shapes using provided guidelines and by connecting dots. These tests assess visual-motor integration, visual perception and motor coordination skills alone. They also assess the relative contribution of visual perception and motor factors in a child's visual motor integration skills and differentiate children with motor skills deficits from those without. (10 minutes)

Memory Measures

California Verbal Learning Test, Children's Version (CVLT-C) [233]: The CVLT-C is a list-learning measure of verbal memory that includes five presentations of a list of 15 words comprising three categories. Learning is evaluated across the five learning trials as well as following a distracter list, short and long delays. Children are also presented with categorical cues and a list of target and non-target words from which they must identify those words presented on the 15 item list. Process scores allow evaluation of encoding, retrieval, retention and recognition abilities. The California Verbal Learning Test, Second Edition (CVLT-II) [234] is a comparable version of the test administered to individuals 17:0 years of age and older. It comprises sixteen words from four semantic categories and provides the same structure, allowing for the examination of encoding, retrieval, retention, and recognition. To reduce practice effects, this measure will only be administered at baseline, 2 years post and 4 years post. (15-20 minutes)

CogState [224, 225]: For the Continuous Paired Associate Learning task, the child is asked to learn and remember figures hidden beneath different locations on the screen. The shapes then appear centrally, and initially all appear peripherally for matching and remembering where each was located. Thereafter, as each picture is revealed centrally, they are required to tap the peripheral location that hides the same shape. Total errors is the outcome measure (~6 minutes).

Processing Speed Measures

Processing Speed Index- WISC-IV: The Coding and Symbol Search subtests from the age appropriate Wechsler scale (WISC-IV or WAIS-IV) will be administered as measures of processing speed.

Motor Measures

Purdue Pegboard: The Purdue Pegboard [235] assesses fine motor speed and dexterity by timing participants as they place pegs in holes on a pegboard.

Participants complete the task first with their dominant hand, next with their non-dominant hand and finally with both hands. (5 minutes)

Academic Achievement Measures

The Woodcock Johnson Tests of Academic Achievement-Third Edition (WJ-III-ACH) [230]: The WJ-III Achievement allows for interpretation of broad and specific academic factors and allows for combining subtests to measure different domains. Selected subtests for this study are described in further detail below.

WJ-III-ACH Word Attack: This task assesses the ability to pronounce pseudo words using phonological decoding skills. (3 minutes)

WJ-III-ACH Letter-Word Identification: This task assesses single letter identification for younger children and word reading for older children, thereby testing basic letter recognition and word reading skills. (5 minutes)

WJ-III-ACH Reading Fluency: This task assesses reading speed. (3 minutes)

WJ-III-ACH Calculation: This task assesses the ability to perform simple to complex mathematical computations. (5-10 minutes)

WJ-III-ACH Math Fluency: This task assesses math calculation speed. (3 minutes)

Bracken Basic Concept Scale, Third Edition, Receptive (BBCS-3:R) [236]: The BBCS-3:R assesses early and emerging academic skills. Five individual subtests assess knowledge of colors, letters, numbers, amounts, and shapes by requiring the child to point to the stimulus requested by the examiner. A School Readiness Composite score is produced. This task is only administered to young children for whom the WJ-III-ACH measures described above are not yet developmentally appropriate. (15 minutes)

Social-Emotional Measures

Behavior Assessment System for Children, Second Edition (BASC-2) [237]: The BASC-2 is a questionnaire assessing behavioral, emotional and adaptive functioning. The parent form contains 10 clinical scales and 6 adaptive indices. The clinical scales include those of the externalizing problems composite (e.g., Hyperactivity, Aggression, Conduct Problems), the internalizing problems composite (e.g., Anxiety, Depression, Somatization), and the behavioral symptoms indices (Atypicality, Withdrawal, and Attention Problems). Adaptive scales include Overall Adaptive Skills, Functional Communication, Activities of Daily Living, Leadership, Social Skills and Adaptability. (15 minutes)

Brief Symptom Inventory (BSI) [238]. The BSI is an inventory used to monitor parental distress and coping. It includes nine symptom scales: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism. From these scales, three global indices are derived- Global Severity Index, Positive Symptom Distress Index and Positive Symptom Total. Parents complete this measure. (8-10 minutes)

Table 1 Neurocognitive Measures by Functional Domain

Cognitive Domain	Measure	Broad Skill	Task Characteristics	Age Range	Admin. Time
Full Scale IQ	1. WPPSI-III (Full Battery)	Early Childhood Global Cognitive Function	Verbal and nonverbal reasoning; Processing speed	WPPSI-III=3-5:11	60 min.
	2. WISC-IV/WAIS-IV (8 subtests)*	Global Cognitive Function	Verbal reasoning (Vocabulary & Similarities), nonverbal reasoning (Block Design & Matrix Reasoning), attention/ working memory (Digit Span & Letter Number Sequencing) & processing speed (Coding & Symbol Search)	WISC-IV=6-16:11 WAIS-IV=17+	60-90 min.
Attention & Executive Function	3. CogState	Attention, Working Memory, Processing Speed	Computerized measure of visual attention (Identification, Detection), working memory (N-back), psychomotor speed (Detection) & executive function (Groton Maze)	5+	15 min.
	4. Wechsler WM Index (Digit Span & Letter Number Sequencing)	Brief Auditory Attention, Auditory Working Memory	Repeating random digits in strands of increasing length both forward and backward; Re-sequencing strands of numbers and letters presented in mixed order.	WISC-IV=6-16:11 WAIS-IV=17+	N/A above
	5. WJ-III-COG Retrieval Fluency	Verbal Fluency	Child produces as many items as possible belonging to a specified category (e.g., animals)	3+	3-5 min.
	6. BRIEF Questionnaire (Parent Measure)	Executive Function	Questionnaire assessing executive dysfunction in community	BRIEF-P=3-5:11 BRIEF=6-18:11 BRIEF-A=19+	15 min.

Visual Spatial/ Visual Motor	7. Beery VMI	Visual Perception, Motor Coordination & Visual-Motor Integration	Blue- Match shapes of decreasing size Green- Draw shapes of increasing complexity Brown- Draw shapes by connecting dots	3+	15 min.
Memory	8. CVLT-C / CVLT-II	Verbal List Learning	Learn a novel word-list through multiple presentations, interference, delay & recognition	CVLT-C=6-16:11 CVLT-II=17+	15 min.

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	9. CogState	Visual Learning	Learn spatial location of hidden objects	6+	5 min.

Processing Speed	10. Wechsler Processing Speed Index (Coding & Symbol Search)	Psychomotor & Processing Speed	Coding- fill-in symbols using a number-symbol code Symbol Search- identify presence of one of two target shapes amongst a group of five search shapes	WISC-IV=6-16:11 WAIS-IV=17+	N/A above
Motor	11. Purdue Pegboard	Fine motor speed & dexterity	Child places pegs in a pegboard as quickly as possible. Scores are obtained for dominant and nondominant hands separately, as well as both hands in coordination.	3+	5 min.
Academic Skills	12. WJ-III-ACH Word Attack, Letter-Word Identification, Reading Fluency, Calculation, Math Fluency	Reading and Math Abilities	Assesses phonologic decoding, single word reading, speeded reading, math computation and speeded calculation relative to child's age and grade level.	6+	20-35 min.
	13. BBCS-3:R	School Readiness Skills	Child identifies early academic concepts such as letters, numbers, colors, and shapes by pointing.	3-5:11	10 min.
Social-Emotional	14. BASC-II (Parent Measure)	Psychosocial Adjustment	Inquires about 9 behavioral domains including attention, conduct problems, anxiety, depression, somatization, etc.	3- 21:11	15 min.
	15. BSI (Parent Measure)	Parent Coping & Distress	A self-report inventory used to monitor parental psychological problems including anxiety, depression, interpersonal sensitivity and somatization.	3-21:11	8-10 min.

Table Abbreviations: WPPSI-III: Wechsler Preschool & Primary Scale of Intelligence, Third Edition; WISC-IV: Wechsler Intelligence Scale for Children, Fourth Edition; WAIS-IV: Wechsler Adult Intelligence Scale, Fourth Edition; WJ-III-COG: Woodcock-Johnson Tests of Cognitive Abilities, Third Edition; BRIEF: Behavior Rating Inventory of Executive Function; VMI: Beery-Buktenica Test of Visual-Motor Integration, Fifth Edition; CVLT-C: California Verbal Learning Test, Children's Version; CVLT-II: California Verbal Learning Test, Second Edition; WJ-III-ACH: Woodcock-Johnson Tests of Achievement, Third Edition; BBCS-3:R: Bracken Basic Concept Scale, Third Edition, Receptive; BASC-II- Behavior Assessment System for Children, Second Edition;

*These subtests allow for the derivation of a full scale IQ as well as the four index scores (Verbal Comprehension, Perceptual Reasoning, Working Memory and Processing Speed), digit span forward (DSF), and digit span backward (DSB).

6.7 Sleep, Fatigue and Quality of Life Measures

Actigraphy, will be collected annually as described in Section 2.4. Symptom Distress, Multidimensional Fatigue Standard Version, Epworth Sleepiness Scale and Peds Brain Tumor QoL Generic Version and Peds QoL Generic Version will be administered at baseline and every 3 months for the first 2 years, then every 6 months to month 60. During radiation the Multidimensional Fatigue Acute, Symptom Distress, and Brain Tumor QoL and Peds QoL Acute version (measuring QoL over the last 7 days) will be administered weekly. Parental proxy will be obtained as indicated or if patient is unable to complete the questionnaires.

Sleep Measures
Wrist Actigraphy: The Micromini Sleep Watch (Ambulatory Monitoring Inc., Ardsley, NY) is a wristwatch-style device that contains a biaxial piezoelectric sensor and a microprocessor with programmable epoch length. The system's accompanying software will be used to compute the sleep characteristics. Sadeh's algorithm (previously validated against polysomnography in children [81, 86] is the basis of the sleep-wake scoring used in the software program. The actigraph will be applied at baseline for a 5 day sleep assessment and at annual visit.

Sleep Diary-Parent/Patient: The sleep diary will be completed daily by the parent or study participant while wearing the actigraphy.

The Peds QL Multidimensional Fatigue Scale: is an 18-item Likert type scale with three subscales which include general fatigue, sleep/rest fatigue and cognitive fatigue. The patient forms are for three different age groups (5 to 7 year olds, 8 to 12 year olds, and 13 to 18 year olds). There is a parent proxy for each child between the ages of 2-18.

The Symptom Distress Scale (SDS): To be completed by children ≥ 7 years of age. The SDS is a 10-item, self-report, Likert type scale developed to measure the patient's degree of discomfort from specific treatment related symptoms (i.e., nausea, sleep disturbances, appetite, etc.). In our previous work using the SDS with adolescents receiving treatment for cancer, the scale achieved coefficient alphas of 0.81 to 0.82. The SDS also was noted to have construct validity, as hypotheses predicting negative relationships with measures of hopefulness, self-esteem, and self-efficacy were all supported. The SDS can be completed in 3 to 5 minutes.

Epworth Sleepiness Scale: To be completed in children ≥ 7 years of age. The ESS is an 8-item questionnaire that rates the probability of falling asleep on a scale of increasing probability from 0 to 3 in eight different situations. A total score of 0-9 is normal, while a score of 10 or greater indicates sleep referral. The ESS has been validated in obstructive sleep apnea through the measurement of

excessive daytime sleepiness. We will obtain a parent proxy report for children ages 4-6.

Quality of Life
The PedsQL Brain Tumor Module is a 24-item Likert-type scale developed to measure health-related quality of life in children and adolescents who are receiving treatment or survivors' of pediatric brain tumors. The module contains six scales and includes cognitive, pain and hurt, movement and balance, procedural anxiety, nausea, and worry. The research participant's forms are for three different age groups (5 to 7 years, 8 to 12 years, and 13 to 18 years). There is a parent form only for research participants between the ages of 2 and 4 years. There is no patient instrument for children younger than 5 years. The PedsQL Brain Tumor Module forms for the research participant and parents have an internal consistency (Cronbach's alpha coefficients of 0.76-0.87 and 0.78-.92, respectively) with construct validity supported through an analysis of the inter-correlations with the Peds QL and Fatigue Scale [239].

The Pediatric Quality of Life Inventory – PedsQL V.4 is a 23-item Likert-type scale developed to measure health-related quality of life in children and adolescents that takes about 4 to6 minutes to complete. This instrument has parallel forms for patient and parent report, including both acute (QOL within the past 7 days) and longer term (QOL within the past 30 days) forms. The patient forms are for three different age groups (5 to 7 years, 8 to 12 years, and 13 to 18 years). There is a parent form only for age group 2 to 4 years. There is no patient instrument for children younger than 5 years. Subscales on the PedsQL V.4 measure the patients' physical, emotional, social, and school functioning. Both patient and parent forms have been found to be internally consistent (Cronbach's alpha coefficients of 0.91 to 0.92, respectively), with clinical validity (i.e., able to distinguish between known groups of patients on and off-therapy) and beginning construct validity (i.e., hypotheses predicting relationships between certain subscales and other indicators of emotional distress, perceived competency, social support/functioning, and academic competence were supported) [240, 241].

6.8 Physical Performance

Physical performance measures will be obtained at baseline, 12, 24, 36, 48 and 60 months. Assessment will take place in the human performance lab located at St. Jude Children's Research Hospital. The lab is staffed with two Master's level Exercise Physiologists with certification as Clinical Exercise Specialists, two Physical Therapists and a post-doctoral student with degrees in physical therapy and rehabilitation science. All personnel are certified in exercise testing and cardiopulmonary resuscitation.

Overall Physical Performance

Because there is a fair amount of disagreement between self-reported and test-based indicators of physical performance, comprehensive evaluations of mobility require both performance based and self-reported indicators of function [242]. In this protocol, we will evaluate overall physical performance with both a measured task sets and patient reported outcomes. Measured task sets will include the Bruninks-Oseretsky Test of Motor Proficiency – Version 2 (Short Form) for those 4-21 years old and the Physical Performance Test for those 22 years old and older. The self-report instruments for will include the Pediatric Physical Function – Mobility Short Form 1 and the Pediatric Physical Function – Upper Extremity – Short Form 1 for those 4-17 years, and the Physical Functioning Short Form 1 for those 18 years and older.

The Bruinicks-Oseretsky Test of Motor Proficiency Version 2 (BOT-2) is norm-referenced and designed to test motor function in children and adolescents 4-21 years of age. The motor composite score describes overall motor abilities and comprises fine motor control, manual coordination, body coordination, strength and agility. We will use the total motor composite from the BOT-2 Short Form to describe overall motor function. Internal consistency reliability coefficients for the BOT-2 total motor composite are 0.95, 0.95 and 0.96 for 4-7, 8-11, and 12-21 year olds, respectively. Test-retest reliability correlation coefficients are 0.83, 0.82, and 0.77 for the three age groups. Inter-rater reliability is extremely high with an overall correlation of 0.98. Scores on the BOT-2 consistently increase with increasing age and have been used to demonstrate differences between healthy children and children with clinical motor deficits. Correlations between the BOT-2 and other tests of motor performance, like the Peabody Developmental Motor Scales (adj. R^2=0.73) and the Test of Visual Motor Skills Revised (adj. R^2=0.74) have been reported. The items on the BOT-2 will be administered and scored according to the standardized procedures in the manual. Standard BOT-2 scores will be used for analysis [243].

To quantify overall physical performance in those 22 years of age and older, participants will be asked to complete the 7-task physical performance test (PPT) [244]. The PPT is reliable (Cronbach's alpha=0.87), with excellent test-retest reliability (r=0.99). It is moderately correlated with several other measures of health and is more sensitive than traditional self-reports in detecting functional loss prior to disability [245, 246]. It includes fine and gross motor components and takes approximately 10 minutes to administer. The PPT was originally tested in the elderly in clinical, residential and institutional settings [244]. A modification of the PPT has been used to compare cancer survivors with normal controls. Controls outperformed cancer survivors in this study by a factor of at least two [247]. Adults with no deficits score a 28/28 on the PPT.

Self-reported physical performance will be evaluated using the Pediatric Physical Function – Mobility Short Form 1 and the Pediatric Physical Function – Upper Extremity – Short Form 1 for those 4-17 years, and the Physical Functioning Short Form1 for those 18 years and older from the Patient-Reported Outcomes

Measurement Information System (PROMIS) (http://www.nihpromis.org/default.aspx), a network of NIH-funded primary research sites and coordinating centers that have worked collaboratively to develop a series of tools to reliably and validly measure patient-reported outcomes (PROs). The instruments selected for our protocol are derived from patient responses to a set of rigorously designed questions about physical functioning. Each instrument has been subjected to a multi-stage development and testing program to ensure that the information meets scientific standards of reliability. The PROMIS instruments are free of charge to enable clinicians and researchers to have access to efficient, precise, valid, and responsive indicators of a person's health status. These measures are available for use across a wide variety of chronic diseases and conditions and in the general population. They are free of charge and can be administered via paper and pencil or as computerized adaptive testing.

Body Composition

Anthropometric measurements, including height by wall mounted stadiometer (without shoes), weight by electronic scale, and waist and hip circumference, will be obtained. Trained clinic staff will measure waist and hip girths (cm) with a non-stretching anthropometric tape directly over the skin. Waist circumference will be measured midway between the anterior superior iliac spine, and the lower rib margin and hip girth will be measured at the maximum hip width. Measurements will be recorded to the nearest 0.5cm. Waist to hip ratio will be calculated by dividing waist by hip circumference. Intra- and inter-rater reliability coefficients are reported at 0.99 for waist and at 0.98 for hip measurements [248]. Waist circumferential measurements have a sensitivity of 85% to correctly classify persons with central adiposity when compared to classifications made by DEXA [249]. These measurements are part of the comprehensive evaluation and will not be treated as individual outcomes. Body weight and/or BMI are used to normalize strength values [250].

Flexibility (Ankle Range of Motion and Sit and Reach)

Ankle dorsiflexion active and passive range of motion will be measured with a goniometer. The goniometer is a reliable and valid measure of active and passive range of motion with standard procedures [251-253]. Normative data have been published by Norkin, Moseley and Baggett [254-256]. Overall flexibility will be measured by having the participant perform the sit and reach test. A yardstick is placed on a firm flat surface and tape is placed across it at a right angle to the 15 inch mark. The participant sits with the yardstick between the legs, with legs extended at right angles to the taped line on the floor. The heels of the feet touch the edge of the taped line and are 10-12 inches apart. The participant reaches forward with both hands as far as possible, and the best value for three trials, in centimeters, at the fingertips is recorded [67, 257, 258]. Reference ranges for typically developing children, adolescents and young adults are available for both of these measures [97, 102, 255, 259].

Balance

Balance will be measured by having the subject complete the sensory organization test (SOT) on a computerized dynamic posturography system (SmartEquitest, Neurocom International). Participants will stand on dual force plates which are pitched up or down in an anterior-posterior direction to provoke ankle motion. The participant stands in an upright position with the medial malleoli positioned directly over the axis of rotation of the force plates. A colored visual screen surrounds the participant on three sides. Visual and kinesthetic inputs are manipulated to create six different conditions, each of which is tested with three 20 second trials. During testing, the device continuously records the participant's center of pressure over the force plates. A difference score is computed from the normal range of anterior-posterior sway (12.5 degrees) and the maximum range of sway of the participant on each trial; that score is expressed as a percentage. The higher the score, the less the participant swayed. A trial ending in a fall (injury prevented because of the safety harness) is scored at zero [260]. Mean data from the three trials under each condition will be used to characterize balance. Reference data are available for typically developing children, adolescents and young adults from the literature and from normal population controls tested in our human performance laboratory [261-269].

Coordination

Fine motor coordination will be measured with the composite cerebellar function severity score and overall coordination with the brief ataxia rating scale. The composite cerebellar function severity score is based on performance on two fine motor tasks. The examination quantifies finger and hand coordination. The first task is the nine-hole pegboard test [270, 271]. The participant is seated and holds nine dowels in one hand. The participant places them, one by one, with the opposite hand, in a board with nine holes. The time begins when the first peg is placed in a hole and ends when the last peg is placed. The second test is the click test. It uses two mechanical counters fixed on a wooden board 39cm apart. The participant is seated in front of a table on which the counters are placed. S/he uses his/her index finger to press the buttons on the counters alternately 10 times each. Timing starts when the first button is depressed and stops when the second counter reads 10. The trial is repeated for each hand [272]. The times to complete each task are converted into age adjusted z-scores and log transformed. Normal scores range from 0.64-0.94 log seconds. The brief ataxia rating scale (BARS) is a modification of the International Cooperative Ataxia Rating Scale (ICARS) designed to be used by neurologists and movement specialists. It includes Gait, Kinetic Function- Arm, Kinetic Function-Leg, Speech, and Eye Movements. It correlates with the Modified ICARS and the Scale for the Assessment and Rating of Ataxia [273] 0.90 and 0.92. Intra-rater and inter-rater reliability (intraclass correlation coefficient) are 0.91 and 0.93 respectively purposes. Reference data are available for both coordination tests [270-272, 274].

Muscle Strength and Power (Knee Extension, Dorsiflexion, and Grip)

Lower extremity strength values will be evaluated with the Biodex III. Participants will be seated for both tests and secured on the padded seat with manufacturer provided positioning straps at the chest, waist, and thigh. Peak torques will be recorded during isometric [175] and isokinetic contractions (60, 120, 180 degrees per second ages 5-12 years, and 60, 180, and 300 degrees per second ages 13 years or older - knee; 30, 60 degrees per second - ankle). Calibration will be performed before each session according to manufacturer's instructions. Subjects will warm up by walking or cycling for 5 minutes prior to testing. Care will be taken to align the anatomical axis of the joint with the mechanical axis of the dynamometer before the tests. Two to four trials will be performed before testing, followed by three maximal voluntary movements. Torque will be corrected for gravitational moments of the lower leg and the lever arm. A rest period of 2 minutes will be allowed between trials to minimize fatigue [275]. We will initially use peak torque values from knee speeds of 60 degrees per second and ankle speeds of 30 degrees per second for analysis as these speeds closely represent power for daily activities like moving sit to stand, climbing stairs and lifting and carrying. Normative values and ranges for children and adults are available from the equipment manufacturer and from previously published data [68, 123, 250, 276-287]. Hand grip strength in kilograms will be measured using a Jamar hand held dynamometer (Sammons Preston Rolyan, Nottinghamshire, UK). Participants will be seated with the shoulder at 0-10 degrees and the elbow in 90 degrees of flexion. The forearm will be positioned in neutral. Each participant will complete three trials, the average used for analysis [288, 289]. Age and gender specific normative data have been published by Mathiowetz et al. [288-290].

Cardiopulmonary fitness

Resting Electrocardiogram *(*ECG): A resting ECG will be completed to examine heart rate, rhythm, hypertrophy, and ischemia to rule out any acute cardiac problems prior to exercise testing. A standard 12 lead electrocardiogram (the Med Graphics Cardio Perfect® Resting/Stress ECG system) will be collected for 15 seconds at 25mm/s with a gain setting of 10mm/V with the patient in a recumbent position.

Resting Energy Expenditure (REE): REE will be measured with indirect calorimetry after an overnight fast. This measurement will be conducted using MedgraphicsUltima Cardio O2® metabolic testing system (E.C. Certificate No. CE 94534). This system collects breath-by-breath measurements of flow, carbon dioxide and oxygen with other calculated gas exchange parameters. Flow is measured with the flow sensor connected to a pair of differential pressure transducers. Flow through the flow sensor causes a pressure differential that generates an electrical signal which is translated into flow and volume calculations. Oxygen analysis is performed via gas fuel cell method. This method has a range of 0 to 100% oxygen saturation; accuracy is 1% of reading across the range, and a response time less than 130 msec [291]. Carbon dioxide is measured with a non-dispersive infrared sensor and chambered gas. This method has a

range of 0 to 15%, accuracy is ± 0.05 %CO_2 and a response time of less than 130msec [292]. The system is capable of sampling and analysis with as little as 0.5 L/min. Gas correlations are verified with known gas concentrations before each test and flow volumes are calibrated once daily with a 3 L syringe.

Following a resting ECG recording, a 5 to 10 minute seated rest period will be given. After the rest period, the patient will be fitted with a neoprene mask with attached pneumotach and sampling lines. The patient will lie in a supine position on an exam table for a 5 to 10 minute "settling in" period. Immediately followed by the "settling in" period, data collection will begin and will consist of 10 minutes of steady state energy expenditure defined as a confidence interval of less than 10% [293]. Once breathing and heart rate are stabilized, VO_2 and VCO_2 will be recorded breath by breath for 10 minutes and averaged for analysis. Respiratory quotient (RQ) will be continuously monitored and averaged for analysis.

Cardiopulmonary Exercise Test (CPET): Maximal cardiopulmonary exercise testing with ECG and breath by breath gas exchange analysis will be completed on a treadmill using the Balke protocol or cycle ergometer using an incremental ramping protocol. During this test, ECG, and gas exchange will be monitored continuously by the previously described systems while blood pressure will be measured every 2 minutes throughout the protocol using the Tango automated system interfaced to the Cardioperfect program. Rating of perceived exertion will be monitored with each blood pressure check using the modified Borg scale with the faces of exertion.

The Balke protocol will be used for the treadmill test will be completed on a Trackmaster 425 [294]. After a light warm up, the protocol will begin with the child walking at 3.5 mph on a 0% graded and increasing incline 2% every 2 minutes until exhaustion. The participant will be instructed to use the rails for balance only and a spotter will be in place in the event of a fall or stumble. This test may be modified by adding initial incline and/or increasing speed for more fit participants with the goal of keeping test duration between 8 and 11 minutes.

A cycle ergometer protocol will be used in those who are unable to complete the treadmill test. A ramp protocol will be chosen based on the participant's current fitness level. For smaller and unfit children, an initial workload of 10 W and an increase of 10 W/min until exhaustion will be used. For older and more fit children, an initial workload of 20 to 25 W and an increase of 20 to 25 W/min will be used [294]. The Lode Corival cycle ergometer is fully adjustable and capable of accommodating small children to adults. The seat height and crank length will be adjusted to create 160 degree knee bend at full extension. The participant will be instructed to maintain a pedaling cadence equal to 50 to 60 rpm. The rpm will be continuously displayed in direct view so the participant has constant feedback and can adjust cadence accordingly.

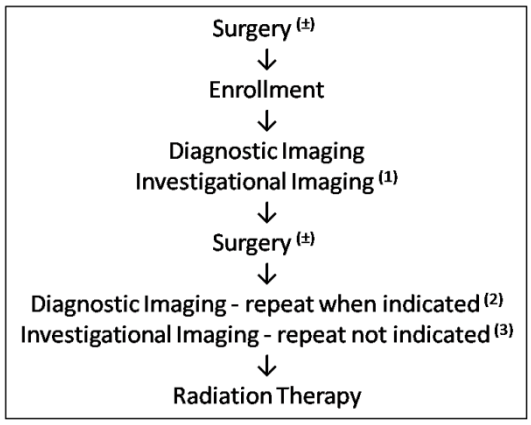
For both modes of CPET, ECG, gas collection, and blood pressure monitoring will begin 5 to 10 minutes pre test and continue until 5 to 10 minutes post test termination. All exercise testing will continue until exhaustion. The CPET will be terminated early if the clinical information indicates that further testing would compromise the patient's health, when the clinical findings are established and additional testing is unlikely to provide more information, and if there is any abnormality or malfunction of testing equipment. The following clinical signs will be used in addition to good clinical judgment to determine termination necessity (304).

- A decrease in ventricular rate with increasing workload associated with symptoms inadequate cardiac output
- Failure of heart rate to increase with exercise and symptoms indicating inadequate cardiac output
- Progressive fall in systolic blood pressure with increasing workload
- Severe hypertension in excess of 250mmHg systolic or 125mmHg diastolic
- Dyspnea the participant finds intolerable
- Symptomatic tachycardia the participant finds intolerable
- Presence of a ≥ 3mm flat or downward sloping ST-segment depression
- Increasing ventricular ectopy with increasing workload, including a > 3- beat run
- Patient requests termination of the study

Normative data for cardiopulmonary testing are available for children, adolescents and adults [102-107].

6.9 Diagnostic and Investigational MR Imaging

6.9.1 General Information



Diagnostic imaging will be performed at enrollment regardless of prior surgery history.

(1) Investigational imaging may be performed at enrollment or deferred until after planned surgery.
(2) Diagnostic imaging should be repeated when indicated after planned surgery and prior to radiation therapy.
(3) Repeating the investigational imaging following planned surgery is not required if performed at the time of enrollment; however, attempted completion of the investigational imaging is expected prior to radiation therapy.

6.9.2 Diagnostic MR Examination

The number of diagnostic imaging studies is similar to the follow-up of newly diagnosed patients. Each patient will have the diagnostic imaging study performed at the time of enrollment. The initial diagnostic study will serve as the baseline evaluation and the dataset to be used to assess for residual disease after surgery and for radiation therapy planning. The diagnostic imaging study will be repeated for those who undergo surgical intervention, when indicated. Diagnostic imaging performed prior to enrollment is considered part of the dataset and critical to this research and the evaluation and treatment of each patient.

The study time point (t=0) will be the first day of radiation therapy. Follow-up MRI will be performed every 3 months for the first 2 years, then 6 month intervals through the end of the fifth year. Optional MRI scan at 27 and 33 month at the discretion of the treating physician.

Diagnostic imaging performed for suspected neurotoxicity should include the standard protocol sequences. Diagnostic imaging performed at unscheduled time points because of concerns regarding toxicity, tumor progression or other reasons will be considered part of the protocol data set even though the methods for these evaluations may not correspond exactly to the protocol. It is suggested that the protocol imaging sequences be used in these unscheduled evaluations.

The core clinical imaging examination will be according to the prevailing St. Jude standard of care. Diffusion tensor imaging and investigational MT imaging will be performed at each follow-up. After the acquisition of four DTI/MT examinations in 15 patients, interim analysis of MT imaging data will be performed. The investigational MT sequence will no longer be performed after 8/1/2020. Perfusion MRI and susceptibility-weighted imaging [295] will be performed once per year. Perfusion MRI will permit evaluation of subtle changes in perfusion, which may accompany microvascular damage undetectable by conventional MR angiographic imaging. Susceptibility-weighted imaging allows the detection and characterization of subtle foci of hemorrhage or mineralization not detectable on conventional sequences. Baseline DTI FA and ADC in brainstem and cerebellar peduncles will be compared to healthy children benchmarks. The time course of DTI FA and ADC changes in brainstem and cerebellar peduncles will be determined. The perfusion of motor and sensory

cortex and tumor will be observed, DTI of white matter tracts will be correlated with neurological outcome.

All clinical and research MR imaging studies will be performed on 3T MR systems unless contraindicated. To facilitate comparisons with magnetization transfer imaging and previously acquired benchmark data in healthy children, examinations performed at St. Jude will be preferentially performed on the 3T Trio system (Siemens, Erlangen Germany), and may be performed at 1.5T if imaging at 3T is contraindicated.

6.9.3 Positron Emission Tomography

Positron emission tomography (PET) will be performed at the time of study entry, 12, 24, and 36 months after the start of radiation therapy. The objective of this study is to correlate PET findings with rate and pattern of failure. The interpretation will include degree of avidity (none, low, moderate, high) and qualitative change when reviewing follow-up studies. The following data will be acquired: 1) metabolic tumor volume at different SUV levels; 2) metabolic activity within MRI defined volumes (target volumes and solid, cystic and combined components); 3) minimum, maximum and mean SUV of the solid component, 4) SUV distributions of the metabolic tumor volume and MRI defined volumes at different time points; and 5) change in parameters over time.

F18-FDG PET will be obtained with the patient NPO for at least 6 hours. Images will be acquired in 3-D mode for 5-15 minutes, 1 hour after the administration of F18-FDG. Radiopharmaceutical dose will be 0.10-0.15 mCi/kg body weight (minimum: 2mCi per dose; maximum: 12mCi per dose). A non-contrast CT scan of the area of interest will be obtained immediately prior to the commencement of PET image acquisition.

6.9.4 MET-PET

MET-PET participants will fast for at least 4 hours prior to the study. Patients are then injected intravenously with 20mCi/1.7 sq m body surface area of ^{11}C-methionine (maximum prescribed dose 20 mCi). The administered dose will be +/- 20% of the prescribed dose due to the rapid decay of ^{11}C-methionine. For doses outside this range, physician documentation is required. A non-contrast CT scan of the area of interest will be obtained immediately prior to the commencement of PET image acquisition. Scanning may begin immediately for dynamic studies using a framing rate to be determined. For non-dynamic studies, scanning may begin ~ 5 minutes after injection for ~15 minutes. Acquired data are reconstructed into multiplanar attenuation and nonattenuation images using standard vendor supplied software.

PET Logistics: In the event of delays which cause the available activity to fall to less than 25% of the prescribed dose, then the decision to proceed will be based

on factors such as ability to reschedule the patient in a timely manner, cyclotron chemistry availability, anesthesia resources, need to commence therapy, etc. The nature of the study allows flexibility. The study can be abbreviated and tailored so that the primary objective can be satisfied without sufficient activity to address the secondary objectives. Image analysis will be performed both qualitatively and semi quantitatively.

PET Analysis: Qualitative analysis will be conducted by the responsible investigators and will consist of visual inspection of the area suspected to contain tumor and comparison with uninvolved nearby tissue. The tumor will be compared with uninvolved brain and the uptake will be graded on a scale comparable to the following: 0=no detectable uptake; 1=uptake present but less than noninvolved background; 2= uptake approximately equal to background; 3=uptake greater than background. Semi-quantitative analysis will be performed include calculation of a standardized uptake value (SUV: activity in the region of interest normalized to participant weight and injected dose) by drawing a region of interest (ROI) over the area suspected to contain tumor.

6.10 Pathology and Biological Studies

6.10.1 Central pathology review

All tumor samples will be submitted for pathology review and biological studies (see below for guidance on submission of tissue to St. Jude Children's Research Hospital).
The purpose of pathology review is to confirm that patients registered on the trial have a diagnosis of ependymoma as follows:

- Classic ependymoma (WHO grade II)
- Anaplastic ependymoma (WHO grade III)

Tumors with a diagnosis of ependymoblastoma and other embryonal tumors or gliomas are not eligible.

Pathology review will be undertaken on submitted unstained sections on slides and tissue scrolls from formalin-fixed paraffin-embedded (FFPE) tissue blocks used to make the initial (first surgery) diagnosis of ependymoma AND on submitted unstained sections on slides and tissue scrolls from FFPE tissue blocks used to confirm a diagnosis of recurrent ependymoma at any subsequent surgical resection. An additional aim of pathology review, in the event of obtaining peritumoral CNS tissue, is assessment of the adverse effects of prior radiation therapy on normal tissues, including blood vessels.

6.10.2 Biological studies

All tumor samples will be submitted for pathology review and biological studies (see below for guidelines on submission of tissue). However, in a situation where tumor samples are limited, the priority will be an accurate pathological diagnosis.

6.10.3 Methods

Biological studies will be undertaken on diagnostic FFPE samples with regard for preserving tumor in the tissue block(s). Tissue archived at initial presentation (first surgery) and obtained at subsequent surgical events for recurrent tumor(s) will be requested.

6.10.4 Preparation and shipment of tissue

Where frozen samples that have been flash-frozen and stored at -80^{o}C or in liquid nitrogen are available, we request 100-200mg of tissue, which should be shipped to the address below on dry ice separately from FFPE tissue.

Whether frozen samples are available or not, we are requesting FFPE tissue blocks as described above for both pathology review and biological studies. If FFPE blocks are submitted, these will be processed rapidly by the SJCRH neuropathology research laboratory and returned to the referring pathology department with adequate tissue for further diagnostic or medicolegal use. FFPE blocks are much preferred, but if they cannot be submitted, we request the following materials from the referring pathology department, which will used for both pathology review and biological studies:

- 20x5µm FFPE sections from a block containing at least a 10x10mm area of tumor without surgical or processing artifacts placed on coated slides (safeguard for antigen retrieval during immunohistochemistry). If a block conforming to these criteria exists and also contains peritumoral CNS parenchyma, then this tissue is preferred.
- 3x20µm FFPE tissue scrolls placed in a single Eppendorf tube.

All samples must be submitted with patient identifiers and information, e.g., pathology accession number, which will identify primary, recurrent and metastatic tumor samples. For the purpose of pathology review, it is also necessary to submit copies of pathology reports from initial diagnosis (first surgery) and subsequent surgical events for recurrent or metastatic disease, from which samples are submitted. This allows confirmation of diagnosis and accurate identification of samples.

For biological studies, all samples will be de-identified and receive a code that will render the samples (link)-anonymized for research aspects of the trial. Frozen tissue samples will be stored in the Tissue Resources Laboratory at SJCRH.

FFPE samples can be shipped overnight at room temperature, along with any venous blood samples, but separate from any frozen samples (see above for guidelines), to the address below.

Tissue samples should be shipped to:
Dr. David Ellison
Dept. of Pathology
St. Jude Children's Research Hospital
262 Danny Thomas Place, MS# 250
Memphis TN 38105
901-595-5438 (tel.)
901-595-3100 (fax.)

It is important to ship samples by FedEx overnight to SJCRH and to avoid shipment dates that will avoid receipt at SJCRH on weekends or US public holidays.

6.10.5 Cytokine Collection

Purpose: Collect and store patient blood for future cytokine measurement.

Procedure for Processing Blood for Cytokine Collection, Storage, and Documentation

1. Verify patient lab order and collection date and time.
2. Use Universal Precautions. Draw blood from patient (blood will be collected in Ambulatory Clinics: A/T, Chili's Center, and TTU).
3. Collect two tubes: one purple top for plasma (EDTA coated) and one red top tube for serum; tube size 5 cc. Collect approximately 4 cc blood for purple top (plasma) and 2 cc blood for red top (serum). Place tubes vertical in ice in hazardous bag. A/T clinic will page (#1223) the research nurse when blood is ready for pick-up. Verify patient name on tube upon pick-up. Print out extra labels for storage tubes. Bring blood tubes w/ labels to Danny Thomas Research Center Room D5031.
4. Wipe tubes with Kimwipe and place in centrifuge (equal and opposite). Spin samples for 20 minutes @ 4,200 rpm at 4° C. Prepare labels while tubes are spinning; total 6 cryogenic tubes per patient; 3 plasma and 3 serum.
5. Put on gloves. After spinning is complete, take tubes out and place on rack on a clean work bench. Purple tube = plasma; red top = serum. Remove plasma and serum by pipetting into cryogenic tubes by the following method:
6. Process plasma (purple top) first. Total of 450 µl plasma will be collected in increments of 150 µl: pipette 150 µl of plasma into each tube until total of 450 µl (pipette 150 µl into each tube x 3).
7. Repeat the process for the serum (red top) for a total of 450 µl per 3 serum tubes.

8. Note: keep volume in 150 µl increments. It may be too difficult to get the full 450 µl in each tube: pipette 450, 300 or 150 µl. Record exact volume of each tube on label. To assist in identifying plasma vs. serum, mark all plasma tube caps (top of tube) with black sharpie marker.
9. Screw top cap on cryogenic tube. Place label on cryo tube with the following information: ID#, patient's name, date collected, plasma vs. serum; quantity in µl, and evaluation time point. Place tubes in order inside Revco storage box. In the storage box, for each patient, place the 3 plasma tubes first followed by the 3 serum tubes. Place Revco box in deep freeze refrigerator set at minus 80° C.

Document

1. Record: document on the Recording Sheet for Cytokine Collection. This recording sheet contains the following: protocol number, patient's name, medical record number, date collected, box number, time point collected (evaluation), number of tubes with quantity in each, and collector's initial.
2. Record: document on the Revco Box Record of Samples (this identifies what is located inside each box).
3. Record: place large Millie lab label with accession number and collection date in cytokine binder in Radiation Oncology research office.
4. Record lab collection and completion in Millie through PathNet Application Bar (AppBar). This will ensure and record the lab completion in Powerchart orders.

6.11 Patient Support

In order to pursue all-inclusive care and support for RERTEP patients, a consultation visit may be scheduled with Quality of Life Services and neuro-oncology. These services will be considered standard of care and unrelated to any protocol testing; no data will be collected from these visits.

Quality of Life Services

Integration of pediatric palliative care for children with relapsed or progressive ependymoma and their families is an integral aspect of the provision of holistic cancer care. Patients on RERTEP may receive consultation with the Quality of Life for All (QOLA) team, and the QOLA team provides longitudinal services and resources to the patient and family throughout their illness trajectory, including at the end of life. The QOLA team is comprised of physicians, nurse practitioners, nurses, and a specialized grief and bereavement psychologist, all of whom are trained in the expert provision of compassionate palliative care and hospice services for children with cancer. The primary goal of the QOLA team is to alleviate or mitigate physical, psychosocial, and spiritual distress experienced by the patient or family. QOLA clinicians are available 24-7 to assist with the management of complex or refractory symptoms, as well as to provide

anticipatory guidance with regards to expected signs and symptoms of disease treatment, progression, and the end of life period. Additionally, QOLA clinicians provide psychosocial support to patients and families during this challenging emotional period, and they collaborate closely with psychology, spiritual care, child life, and social work to optimize psychosocial services for patients and families. QOLA clinicians also assist with care coordination across diverse care locations, including coordination of community-based palliative care and hospice services and resources, and they remain available 24-7 to provide guidance via telephone to patients, families, and local palliative care teams and hospice agencies to ensure high-quality care at every stage of the illness experience.

Neuro-Oncology

With permission of the patient or parent, a consultation will be scheduled with the neuro-oncology service to discuss treatment options in addition to re-irradiation. The purpose of the consultation will be provision of information and will not infer that systemic therapy will be provided or administered by the consulting unit. The goal will be to ensure that the patient or their parents understand available treatment options.

Table 6.0.1 Evaluations at Baseline and Follow-up (Prior to Amendment 2.0)

Evaluations/Schedule[1]	**Months after RT Start**													
	0	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**42**	**48**	**54**	**60**
Imaging														
Diagnostic/Investigational MR	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MR Spine[4]	X			X			X			X		X		X
FDG-PET[6]	X			X			X			X				
PET-methionine[6, 7]	X			X			X			X				
Lateral skull X-ray	X													
Bone Age/Q-CT/DEXA	X													
Clinical-Standard														
Assessment/Triage	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam‡#	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lab: CBC‡	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lab: Chemistry‡	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lab: Endocrine Screen‡	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Audiometry[2]‡	X			X			X			X		X		X
Endocrine Clinic‡	X			X			X			X		X		X
Neurology Clinic‡	X			X			X			X		X		X
Ophthalmology‡	X			X			X			X		X		X
CSF Cytology[5]	X													
Clinical-Investigational														
Endocrine/Provocative[3]	X			X			X							
Psychology	X			X			X			X		X		X
Function Laboratory	X			X			X			X		X		X

Sleep/Fatigue Research														
Actigraphy	X			X			X			X		X		X
Questionnaires/QOL	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory-Investigational														
Genomics	X													
Cytokines[7]	X			X			X			X		X		X

*Patient of childbearing potential requires a negative pregnancy test prior to starting treatment. (‡) should be repeated if clinically indicated following craniotomy. [1]Imaging and clinical tests should be performed prior to radiation therapy; however, logistics may make it difficult to complete all exams prior to treatment. The principal investigator reserves the right to accept pre-irradiation testing within 16 weeks of the initiation of radiation therapy. PET-FDG and PET-methionine will also be done at time of progression or recurrence if prior to 24 months. Assessment/triage includes neck and abdomen circumference. #Edinburgh Handedness Inventory performed once. [2]Patients who are unable to undergo standard audiometry may undergo ABR at the treating physician's discretion. [3]Provocative screening will not be conducted for patients when the number of days off corticosteroids prior to the test date is less than the number of days on corticosteroids prior to discontinuance.[4]MR spine may be performed more frequently for patients with spinal metastatic disease or at the discretion of the treating physician. [5]Lumbar puncture for CSF cytology may be waived with PI approval based on contraindication or if adequate evaluation was performed within 3 weeks of enrollment. [6]MET PET and FDG-PET scans not performed at 12, 24 or 36 month evaluation may be performed at a subsequent follow-up evaluation. All METPET studies will be whole-body regardless of the presence or absence of metastatic disease at the time of enrollment. [7]Test will not be collected after July 1, 2020

Table 6.0.2 Evaluations at Baseline and Follow-up at St. Jude (Amendment 2.0)

Evaluations/Schedule[1]	Months after RT Start																
	0	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27****	**30**	**33****	**36**	**42**	**48**	**54**	**60**
Imaging																	
Diagnostic/Investigational MR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MR Spine[4]	X				X				X				X		X		X
FDG-PET[6]	X				X				X				X				
PET-methionine[6, 9]	X				X				X				X				
Lateral skull X-ray	X																
Bone Age/Q-CT/DEXA[7]	X																
Clinical-Standard																	
Assessment/Triage	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam‡#	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lab: CBC‡	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lab: Chemistry‡	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lab: Endocrine Screen‡	X		X		X		X		X	X	X	X	X	X	X	X	X
Audiometry[2]‡	X				X				X				X		X		X
Endocrine Clinic‡	X				X				X				X		X		X
Neurology Clinic‡	X				X				X				X		X		X
Ophthalmology‡	X				X				X				X		X		X
CSF Cytology[5]	X																
Clinical-Investigational																	
Endocrine/Provocative[3]	X				X				X								
Psychology	X				X				X				X		X		X
Function Laboratory	X				X				X				X		X		X
Sleep/Fatigue Research																	
Actigraphy	X				X				X				X		X		X
Questionnaires/QOL	X	X	X	X	X	X	X	X	X		X		X	X	X	X	X
Laboratory-Investigational																	
Genomics	X																
Cytokines[8, 9]	X				X				X				X		X		X

*Patient of childbearing potential requires a negative pregnancy test prior to starting treatment. (‡) should be repeated if clinically indicated following craniotomy. [1]Imaging and clinical tests should be performed prior to radiation therapy; however, logistics may make it difficult to complete all exams prior to treatment. The principal investigator reserves the right to accept pre-irradiation testing within 16 weeks of the initiation of radiation therapy. PET-FDG and PET-methionine will also be done at time of progression or recurrence if prior to 24 months. Assessment/triage includes neck and abdomen circumference. #Edinburgh Handedness Inventory performed once. [2]Patients who are unable to undergo standard audiometry may undergo ABR at the treating physician's discretion. [3]Provocative screening will not be conducted for patients when the number of days off corticosteroids prior to the test date is less than the number of days on corticosteroids prior to discontinuance.[4]MR spine may be performed more frequently for patients with spinal metastatic disease or at the discretion of the treating physician. [5]Lumbar puncture for CSF cytology may be waived with PI approval based on contraindication or if adequate evaluation was performed within 3 weeks of enrollment. [6]MET PET and FDG-PET scans not performed at 12, 24 or 36 month evaluation may be performed at a subsequent follow-up evaluation. All METPET studies will be whole-body regardless of the presence or absence

of metastatic disease at the time of enrollment. [7]Patient must be > 3 years of age. [8]For patients enrolled before August 30, 2019
[9]Test will not be collected after July 1, 2020 **Optional at the dicretion of the treating physician

Table 6.0.3 Evaluations during Radiation Therapy at St. Jude

Evaluation	Week on therapy						
	1	2	3	4	5	6	7
Imaging							
Activation PET*	X	X	X	X	X	X	X
Clinical-Standard							
Physical examination	X	X	X	X	X	X	X
CBC			X				
Chemistry			X				
Clinical-Investigational							
QOL			X			X	
Toxicity Assessment	X	X	X	X	X	X	X
Laboratory-Investigational							
Cytokines[1]			X			X	

*frequency depending on feasibility and availability
[1]For patients enrolled before August 30, 2019

7.0 EVALUATION CRITERIA

In the setting of high-dose irradiation, tumor and normal tissue responses observed on imaging (MR and PET) may mimic tumor progression or present a mixed picture that might include a range of responses including tumor progression, tumor pseudo progression or necrosis. Key to the evaluation of response is timing relative to treatment, history of prior treatment(s) and toxicity, and the presence or absence and volume of residual disease. Disease progression should not be based on a single imaging examination time point, rather definitive evidence of unrelenting tumor progression. In the setting of high-dose irradiation, the specter of necrosis and the urgency associated with intervention and mitigating the consequences of parenchymal and vascular damage requires serial and multimodality imaging examinations at short intervals. The investigator has the option of repeating the MRI, earlier than the next scheduled follow-up, to confirm disease progression, necrosis or in considering surgery to document the same. Disease progression and response will be determined using conventional MR imaging sequences.

<u>Response Criteria</u>

- Complete Response: the disappearance of all neuroimaging-discernable tumor.
- Partial Response: A greater than 50% decrease in the product of the perpendicular diameters of the tumor measured relative to the baseline evaluation, without the appearance of any new areas of disease.
- Stable Disease: A less than 50% decrease in the product of the perpendicular diameters of the tumor relative to the baseline evaluation, without the appearance of any new areas of disease. For patients treated following gross-total resection, stable disease is defined as the lack of appearance of any new discernable tumor.
- Progressive Disease: Greater than 25% increase in the product of the perpendicular diameters of the tumor relative to the baseline evaluation or the appearance of any new areas of disease. Progression of disease is characterized similarly with an increase noted on successive imaging 3-6 months after the study which first demonstrated tumor area or volume enlargement of more than 25%. Cystic enlargement is not considered to be progression of disease. Investigators may elect to repeat imaging earlier that the next scheduled follow-up or wait until the next scheduled follow-up to declare progression.

Necrosis

Necrosis will be defined by enhancement of normal tissues as assessed by contrast-enhanced T1-weighted MR imaging, increased signal on T2 and FLAIR imaging, and the imaging parameters of apparent diffusion coefficient, fractional anisotropy, FDG-PET, and MR spectroscopy, when available. The gold standard to diagnose radiation necrosis has been biopsy; however, surgical intervention may increase morbidity, especially when considering the brainstem and cerebellum. Several imaging modalities have been investigated for their ability to diagnose necrosis and distinguish between necrosis and recurrent tumor. We will rely on serial changes, including increasing parenchymal enhancement on post-contrast T1 images and increasing volume of T2-weighted MR imaging signal abnormality and symptoms to grade necrosis according to the CTCAE v4.0. We have found that resolution of necrosis can be a long process during which lesions can show signs of improvement followed by progression in the same or other sites before stabilizing. According to the CTCAE v4.0 terminology, CNS necrosis has five grades: (1) asymptomatic; clinical or diagnostic observations only; intervention not indicated, (2) moderate symptoms; corticosteroids indicated, (3) severe symptoms; medical intervention indicated, (4) life-threatening consequences; urgent intervention indicated, (5) death. We anticipate that the rate of CNS necrosis (CTCAE v4.0 > grade 3) will be greater than 5% and less than 20% when estimated at one year. The lower bound of this estimate is based on our published data for patients treated in the primary setting [6, 137, 296]. The upper bound of this estimate is empiric. Asymptomatic patients with grade 1 necrosis referred for hyperbaric oxygen or other interventions to prevent progression of

imaging findings and the potential development of symptoms will be scored as grade 1 with supportive documentation.

8.0 REMOVAL FROM PROTOCOL AND OFF-STUDY CRITERIA

The survival for all participants will be followed on study until their death unless they or their parents request that no further information be made available to this study group.

For participants who are treated at collaborating institutions it is recommended that each patient to be taken off protocol be discussed with the PI of the study and if needed, pertinent studies should be sent to the PI for review.

8.1 Off-Study Criteria:

- Parent/Patient request
- Death
- PI discretion
- Lost to follow-up
- Protocol compliance
- Study completion
- Treatment with chemotherapy during the administration of radiation therapy
- Disease progression

8.2 Collaborating Sites Notification

Collaborating institutions should enter an off-study date into CRIS database, accompanied by emailing a copy of the clinic/progress note documenting the reason the participant was taken off study to RadiationOncology-CRA@STJUDE.ORG.

9.0 SAFETY AND ADVERSE EVENT REPORTING REQUIREMENTS

9.1 Reporting Adverse Experiences and Deaths to St. Jude IRB

9.1.1 Only “unanticipated problems involving risks to participants or others” referred to hereafter as “unanticipated problems” are required to be reported to the St. Jude IRB promptly, but in no event later than 10 working days after the investigator first learns of the unanticipated problem. Regardless of whether the event is internal or external (for example, an IND safety report by the sponsor pursuant to 21 CFR 312.32); only adverse events that constitute unanticipated

problems are reportable to the St. Jude IRB. As further described in the definition of unanticipated problem, this includes any event that in the PI's opinion was:

- Unexpected (in terms of nature, severity, or frequency) given 1) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, as well as other relevant information available about the research; 2) the observed rate of occurrence (compared to a credible baseline for comparison); and 3) the characteristics of the subject population being studied; and
- Related or possibly related to participation in the research; and
- Serious; or if not serious suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

  Unrelated, expected deaths do not require reporting to the IRB. Though death is "serious", the event must meet the other two requirements of "related or possibly related" and "unexpected/unanticipated" to be considered reportable.

  Deaths meeting reporting requirements are to be reported immediately to the St. Jude IRB, but in no event later than 48 hours after the investigator first learns of the death.

9.1.2 The following definitions apply with respect to reporting adverse experiences:

9.1.2.1 Serious Adverse Event (SAE): Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include: any substantial disruption of the ability to conduct normal life functions, allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse), a congenital anomaly/birth defect, secondary or concurrent cancer, medication overdose, or is any medical event which requires treatment to prevent any of the medical outcomes previously listed.

For the purpose of this protocol, the following events will NOT be considered serious or unexpected adverse events:

- Radiation Dermatitis, Dry skin
- Pain due to Radiation
- Mucositis
- Nausea, Vomiting, Loss of appetite, Fatigue
- Hair loss
- New or recurrent neurological systems such as swelling of the brain
- Cyst enlargement
- Stroke occurring after completion of radiation therapy
- Secondary tumors occurring after completion of radiation therapy
- Hormone deficiencies
- Events relating to hypothalamic obesity, precocious puberty or diabetes insipidus
- Loss of hearing, vision or neurological function and seizure
- Death unequivocally related to disease progression; hospitalization for treatment of expected signs or symptoms of disease complications (shunt placement and revisions, cyst decompression) or progression of disease
- Wound infection or dehiscences from surgery
- Necrosis

9.1.2.2 Unexpected Adverse Event:

- Any adverse event for which the specificity or severity is not consistent with the protocol-related documents, including the applicable investigator brochure, IRB approved consent form, Investigational New Drug (IND) or Investigational Device Exemption (IDE) application, or other relevant sources of information, such as product labeling and package inserts; or if it does appear in such documents, an event in which the specificity, severity or duration is not consistent with the risk information included therein; or
- The observed rate of occurrence is a clinically significant increase in the expected rate (based on a credible baseline rate for comparison); or
- The occurrence is not consistent with the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

9.1.2.3 Internal Events: Events experienced by a research participant enrolled at a site under the jurisdiction of St. Jude IRB for either multicenter or single-center research projects.

9.1.2.4 External Events: Events experienced by participants enrolled at a site external to the jurisdiction of the St. Jude Institutional Review Board (IRB) or in a study for which St. Jude is not the coordinating center or the IRB of record.

9.1.2.5 Unanticipated Problem Involving Risks to Subjects or Others: An unanticipated problem involving risks to subjects or others is an event which was not expected to occur and which increases the degree of risk posed to research participants. Such events, in general, meet all of the following criteria:

- unexpected;
- related or possibly related to participation in the research; and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. An unanticipated problem involving risk to subjects or others may exist even when actual harm does not occur to any participant.

9.1.3 Consistent with FDA and OHRP guidance on reporting unanticipated problems and adverse events to IRBs, the St. Jude IRB does not require the submission of external events, for example, IND safety reports, nor is a summary of such events/reports required; however, if an event giving rise to an IND safety or other external event report constitutes an "unanticipated problem involving risks to subjects or others" it must be reported in accordance with this policy. In general, to be reportable external events need to have implications for the conduct of the study (for example, requiring a significant and usually safety-related change in the protocol and/or informed consent form).

9.1.4 Although some adverse events will qualify as unanticipated problems involving risks to subjects or others, some will not; and there may be other unanticipated problems that go beyond the definitions of serious and/or unexpected adverse events. Examples of unanticipated problems involving risks to subjects or others include:

- Improperly staging a participant's tumor resulting in the participant being assigned to an incorrect arm of the research study;
- The theft of a research computer containing confidential subject information (breach of confidentiality); and
- The contamination of a study drug. Unanticipated problems generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.

9.2 Serious Adverse Events (SAE) or Adverse Events (AE) felt to be related to ^{11}C-methionine (IND #104987)

Participants will be carefully monitored and adverse events collected using the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE) during active participation of the ^{11}C-methionine PET scan. Active participation is defined as: from time of injection through one hour post injection of ^{11}C-methionine. Vital signs (BP, RR, HR) will be assessed prior to receiving the

injection and at the end of the MET PET scan. Participants will be watched continuously via an in-room camera during the scan.

REPORTING REQUIREMENTS:

Office of Human Subjects' Protection (OHSP): The non-serious adverse events occurring during active participation will be reported to the OHSP in the continuing review reports. In addition to the continuing review reports to the Institutional Review Board, known as the Office of Human Subjects' Protection (OHSP), the principal investigator is responsible for the expeditious reporting of all serious, unexpected adverse events (AEs) involving research participants that occur during active participation. All adverse events occurring outside of active participation (injection to one hour post injection) will follow reporting rules set in Section 9.1.

Serious Adverse Events (SAEs) occurring during active participation that are unexpected-fatal or unexpected-life threatening are to be reported to the OHSP immediately, but every effort will be made to assure it is no later than 48 hours of notification of the event to the principal investigator or designees. All other unexpected (non-fatal or non-life threatening) SAEs occurring during active participation will be reported as soon as possible but within 10 working days of notification of the event. All other SAEs occurring outside of active participation will be reported according to the reporting rules in 9.1.

The SAE of expected death for all on study participants will be reported to the OHSP as soon as possible but no later than approximately 3 working days upon notification of event to the principal investigator or designees. Expected, life threatening SAEs noted during active participation will be reported to the OHSP as soon as possible but no later than 10 working days of notification of the event to the principal investigator or designees. All other SAEs (expected and non-life threatening) and captured AEs occurring during active participation will be reported to the IRB in the continuing review reports.

The term "life threatening" refers to any adverse experience that places the research participant, in the view of the investigator, at immediate risk of death from the reaction, as it occurred, not an event that hypothetically might have caused death if it occurred in a more severe form.

U.S. Food and Drug Administration (FDA): The study will be conducted under IND authorization. Any unexpected fatal or unexpected life-threatening event judged by the principal investigator to possibly be due to the investigational agent/radiopharmaceutical, will be reported to the FDA by telephone or fax as soon as possible but no later than 7 calendar days after notification of the event and followed by a written safety report as complete as possible within 8 additional calendar days (i.e., full report 15 calendar days total after notification of event).

Unexpected, non-fatal and non-life-threatening SAEs, which occur in on-study, participants during the time period of active participation that are considered due to or possibly due to the injection of the radiopharmaceutical agent, will be reported to the FDA by written safety report as soon as possible but no later than 15 calendar days of the notification of the occurrence of the event. Expected SAEs, and unexpected fatal SAEs considered by the principal investigator to be unrelated to the study, will be reported to the FDA in the Annual Review Report along with non-serious AEs. All FDA correspondence and reporting will be conducted through the St. Jude Regulatory Affairs Office.

Copies of all correspondence to the St. Jude IRB, including SAE reports, are provided to the St. Jude Regulatory Affairs Office. All FDA related correspondence and reporting will be conducted through the Regulatory Affairs Office.

Continuing review reports of protocol progress and summaries of adverse events will be filed with the St. Jude OHSP, St. Jude Clinical Protocol Scientific Review and Monitoring Committee (CPSRMC), and FDA at least annually.

9.3 Recording Adverse Events and Serious Adverse Events

Adverse events (AEs) will be evaluated and documented by the clinical staff and investigators and graded using the scoring system according to the NCI Common Toxicity Criteria v4.0. Only the radiotherapy-related adverse events will be collected and scored. Adverse events will be reported per institutional policy. Both serious and unexpected adverse events (Grade 3-5) will be reported through the St. Jude TRACKS (Total Research and Knowledge System) system. Toxicity grading will be determined by the PI, radiation oncologist or neurosurgeon utilizing the pertinent patient history, physical exam and imaging studies. These events will be reported expeditiously to the St. Jude IRB within the timeframes as described above. Cumulative summary of Grade 3-5 events will be reported as part of the progress reports to IRB at the time of continuing review. Specific data entry instructions for AEs and other protocol-related data will be documented in protocol-specific data entry guidelines that have been developed and maintained by study team and clinical research informatics. CRAs are responsible for reviewing documentation related to AEs and entering directly into CRIS protocol-specific database.

9.4 Process for Reporting Adverse Events from and to Collaborative Sites

Adverse events occurring in patients enrolled by collaborating sites will also be reviewed by the PI and discussed in study team meetings. SAE reports from collaborating sites for AEs that are serious, unexpected, and at least possibly related to protocol treatment or interventions will be reported to the site's IRB per the site's local reporting and timeline requirements and to Dr. Merchant at St. Jude within the reporting requirements.

The PI will determine if the event needs to be reported expeditiously to all participating sites, considering the following criteria:

• Is the AE serious, unexpected, and related or possibly related to participation in the research?
• Is the AE expected, but occurring at a significantly higher frequency or severity than expected?
• Is this an AE that is unexpected (regardless of severity that may alter the IRB's analysis of the risk versus potential benefit of the research and, as a result, warrant consideration of substantive changes in the research protocol or informed consent process/document?

If the event does not require expeditious reporting to all sites, it will be included in the annual continuing review.

The PI will report all SAEs reported by collaborating sites to the St. Jude IRB using the "Reportable Event" in St. Jude TRACKS application per the timelines outlined in section 9.1.1 The PI will indicate if all sites should be notified to report to their IRBs, and if the protocol and/or consent should be amended (consent will be amended if event is information that should be communicated to currently enrolled subjects). Generally, only events that warrant an amendment to the protocol and/or consent will be reported expeditiously to all sites. However, any event may be reported expeditiously to all sites at the discretion of the PI.

9.4.1 Reporting Timelines:

For Collaborating Sites: Serious AND unexpected AND related events are to be reported to the St. Jude PI (Dr. Thomas E Merchant, DO, PhD) within five (5) working days of event awareness via fax or email. Unexpected deaths must be reported to the St. Jude PI via phone call or email within 24 hours of the event. A written report using the St. Jude "External Unanticipated Problem/Adverse Event Report" form available from the collaborative sites website must follow.

9.5 Radiation Safety Committee

Initial approval is not required**.**

10.0 DATA COLLECTION, STUDY MONITORING, AND CONFIDENTIALITY

10.1 Data Collection

10.1.1 Electronic case report forms (eCRFs) will be completed by the SJCRH Radiation Oncology CRAs. Data will be entered into a secure database (CRIS) developed and maintained by St. Jude Clinical Research Informatics.

10.1.2 Data Collection Instructions for Collaborative Sites

Collaborating sites will collect data using e-CRFs via remote electronic data entry using the CRIS database. Protocol-specific data and adverse events will be recorded by the collaborating sites' clinical research associates ideally within 2 weeks of completion.

10.2 Study Monitoring

<u>High Risk 3 (HR-3) –</u> Phase II or Phase III Therapeutic Studies with an IND or IDE

The Eligibility Coordinators will verify 100% of the informed consent documentation on all participants and verify 100% of St. Jude participants' eligibility status within 10 working days of the completion of enrollment.

The study team will meet at appropriate intervals to review case histories or quality summaries on participants.

The Clinical Research Monitor will assess protocol and regulatory compliance as well as the accuracy and completeness of all data points for the first 2 participants then 15% of study enrollees every 6 months. Accrual will be tracked continuously for studies that have strata. All SAE reports will be monitored for type, grade, attribution, duration, timeliness and appropriateness on all study participants *semi-annually.*

The monitor will also verify 100% of all data points on the first 2 participants and on 15% of cases thereafter. Protocol compliance monitoring will include participant status, eligibility, the informed consent process, demographics, staging, study objectives, subgroup assignment, treatments, evaluations, responses, participant protocol status, off-study, and off-therapy criteria. The Monitor will generate a formal report which is shared with the Principal Investigator (PI), study team and the Internal Monitoring Committee (IMC).

Monitoring may be conducted more frequently if deemed necessary by the CPDMO or the IMC.

Continuing reviews by the IRB and CT-SRC will occur at least annually. In addition, SAE reports in TRACKS are reviewed in a timely manner by the IRB/ OHSP.

St. Jude collaborating study sites will be monitored on-site by a representative of St. Jude at intervals specified in the Data and Safety Monitoring Plan. International collaborators will be monitored according to the study-specific monitoring plan.

10.3 Confidentiality

Source documents from the study, which identify the study participant, will be kept confidential in a secured area and a password-protected database.

11.0 STATISTICAL CONSIDERATIONS

The primary objective of this protocol is to prospectively estimate the PFS and OS distributions of children and young adults after a second course of irradiation and to demonstrate that many of these patients may be safely salvaged, if additional surgery and radiation therapy are administered. PFS and OS distributions will be measured from the initiation of re-irradiation. The historical data discussed below are retrospective and without correlative neuropsychological and quality of life information; thus, the data are not sufficiently convincing for most investigators.

To conduct this trial, we expect that a high percentage of patients will have received chemotherapy post progression and prior to registering on this trial. The primary objective will be assessed without regard to whether patients did or did not receive prior chemotherapy. However, the potential association of primary outcome with specific chemotherapy given prior to re-irradiation will be explored (exploratory objective 1.3.4).

Historical Data and Analyses

These analyses should be interpreted as exploratory and p-values are to be interpreted descriptively and are not adjusted for multiple comparisons. Patients with ependymoma who experience initial failure may be characterized based on their pattern of failure type (POF_1 = local failure, POF_2 = distant or POF_3 = combined). We analyzed 50 patients previously retreated between 2000 and 2011 according to their retreatment strategy. Possible retreatment strategies include focal retreatment, which was used only for patients with local failures (RT_{2focal}), and craniospinal irradiation with focal irradiation of the metastatic site(s) and primary site when indicated (RT_{2CSI}). RT_{2CSI} was used for all patients with combined or distant failure and selected patients with local only failure

Table 11.0 Pattern of Failure and Treatment Strategy for Historical Cohort

Retreatment Group	Initial Pattern of Failure	Retreatment Strategy	N
A	POF_1 = local	RT_{2focal} = focal irradiation	**22**
B	POF_1 = local	RT_{2CSI} = craniospinal irradiation	**7**
C	POF_2 = distant	RT_{2CSI}	**16**
D	POF_3 = local + distant	RT_{2CSI}	**5**
Total			**50**

The following figure and table provide Kaplan-Meier estimates of the distributions of Progression-Free Survival and Overall Survival for the 50 patients in the historical cohort. PFS and OS are measured from the date of re-irradiation (RT2) until failure (relapse, disease progression, second malignancy or death) or death, respectively. Patients who have not failed are censored at their last date of contact.

Figure 11.1 Progression-free and Overall Survival Historical Cohort

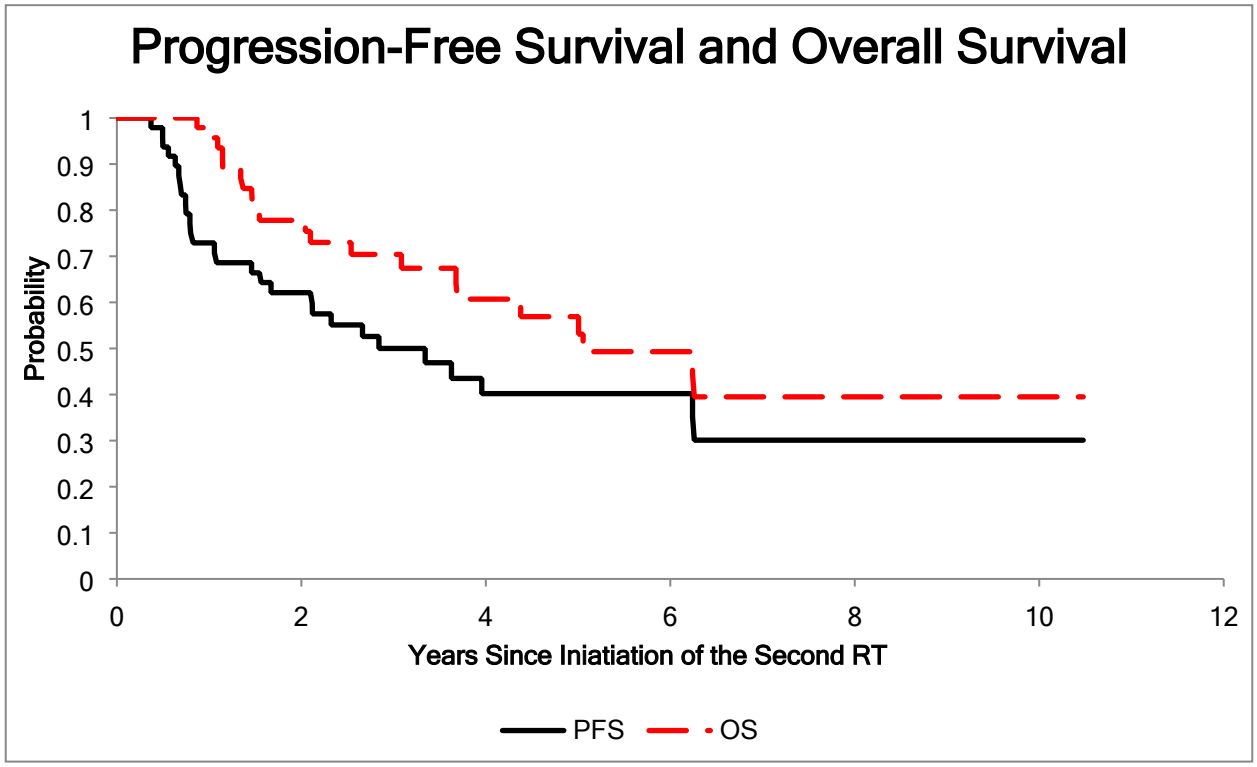


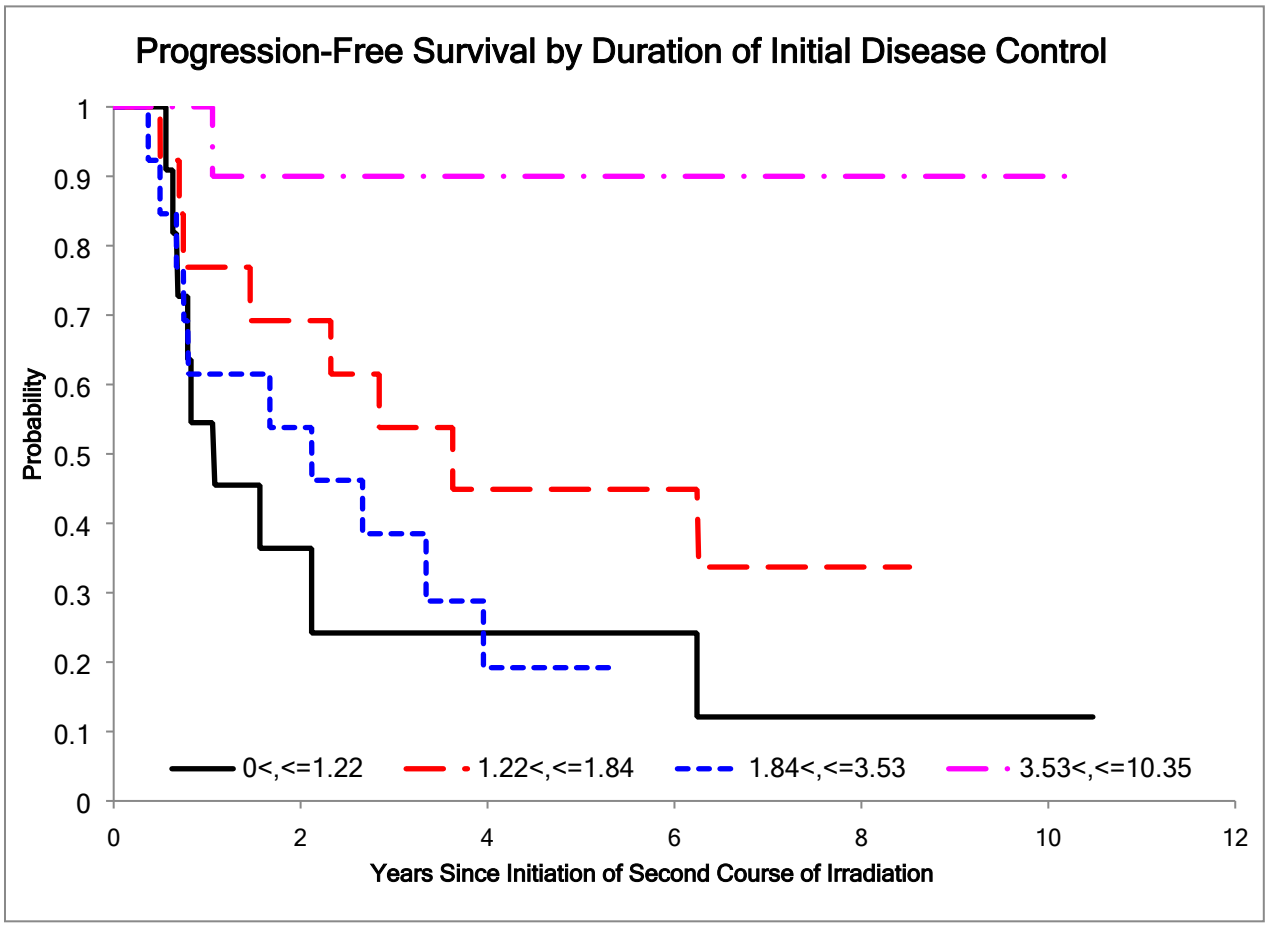
Table 11.1 PFS and OS for the Historical Cohort

PFS						OS					
Years Since Iniatiation of RT2	Risk	Fail	Cens	Prob	SE	Years Since Iniatiation of RT2	Risk	Fail	Cens	Prob	SE
0	50	0	0	1.000	0.000	0	50	0	0	1.000	0.000
1	50	13	3	0.729	0.064	1	50	1	3	0.979	0.021
2	34	5	2	0.621	0.072	2	46	9	5	0.778	0.064
3	27	5	4	0.500	0.081	3	32	3	5	0.704	0.077
4	18	3	3	0.402	0.086	4	24	3	3	0.607	0.087
5	12	0	2	0.402	0.094	5	18	1	2	0.569	0.093
6	10	0	1	0.402	0.098	6	15	2	2	0.493	0.101
7	9	2	2	0.301	0.103	7	11	2	4	0.395	0.125
8	5	0	1	0.301	0.113	8	5	0	1	0.395	0.137
9	4	0	2	0.301	0.145	9	4	0	2	0.395	0.177
11	2	0	2	0.301	0.252	11	2	0	2	0.395	0.307

Descriptive statistics of the duration of initial disease control measured in years from the date of initial irradiation (RT1) until failure is shown in the next table.

	N	Mean	Std	Min	25th %	Median	75th %	Max
Duration of Initial Disease Control In Years	50	2.63	2.24	0.23	1.22	1.84	3.53	10.35

Kaplan-Meier estimates of the PFS after re-irradiation, by quartile of initial disease control, are shown in the following figure. Of the patients whose initial disease control was at least 3.53 years, only one has experienced disease progression after re-irradiation. The p-value for a log-rank comparison of the four groups is 0.0101.



The following Cox models also suggest that duration of initial disease control is associated with duration of PFS and OS after re-irradiation.

Cox Model of PFS for Duration of Initial Disease Control						
Number of Patients (events)	Parameter Estimate	Standard Error	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
50 (28)	-0.379	0.157	0.0159	0.685	0.503	0.932

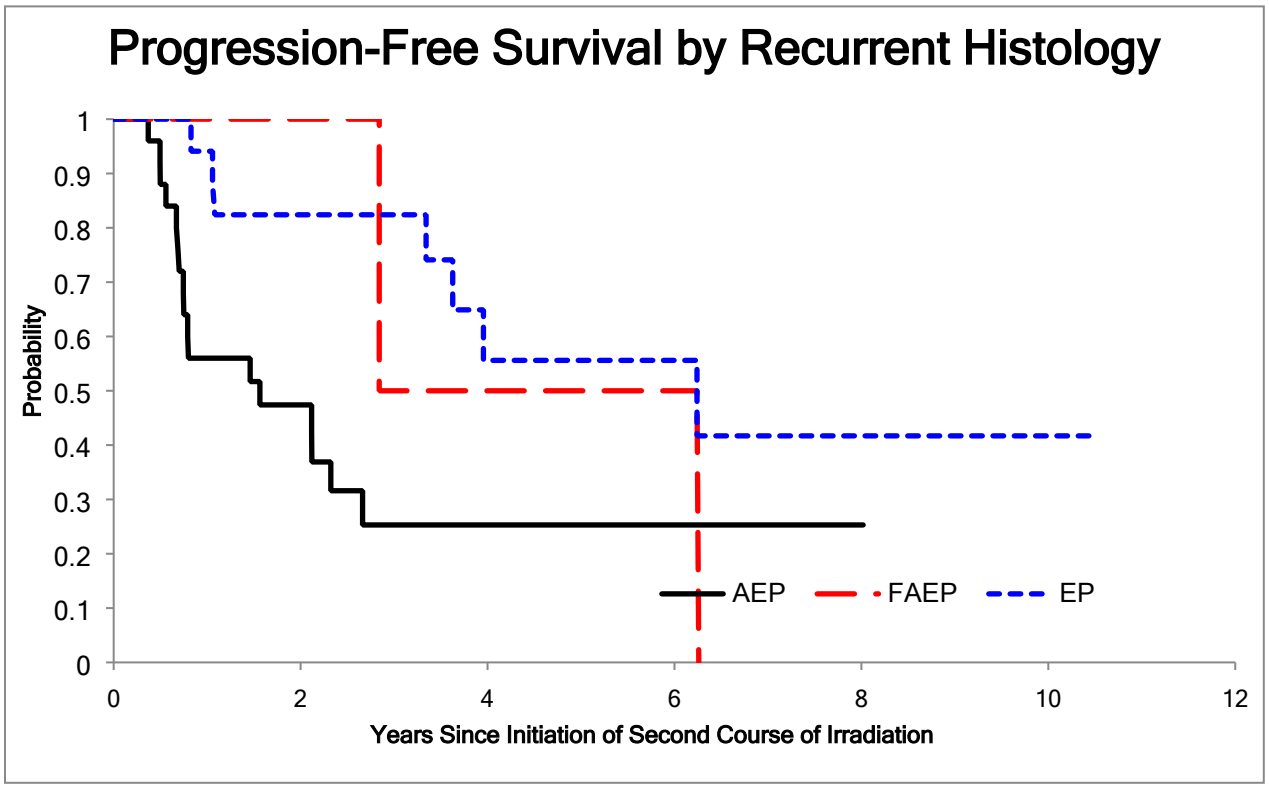
Cox Model of OS for Duration of Initial Disease Control						
Number of Patients (events)	Parameter Estimate	Standard Error	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
50 (21)	-0.743	0.281	0.0081	0.476	0.275	0.825

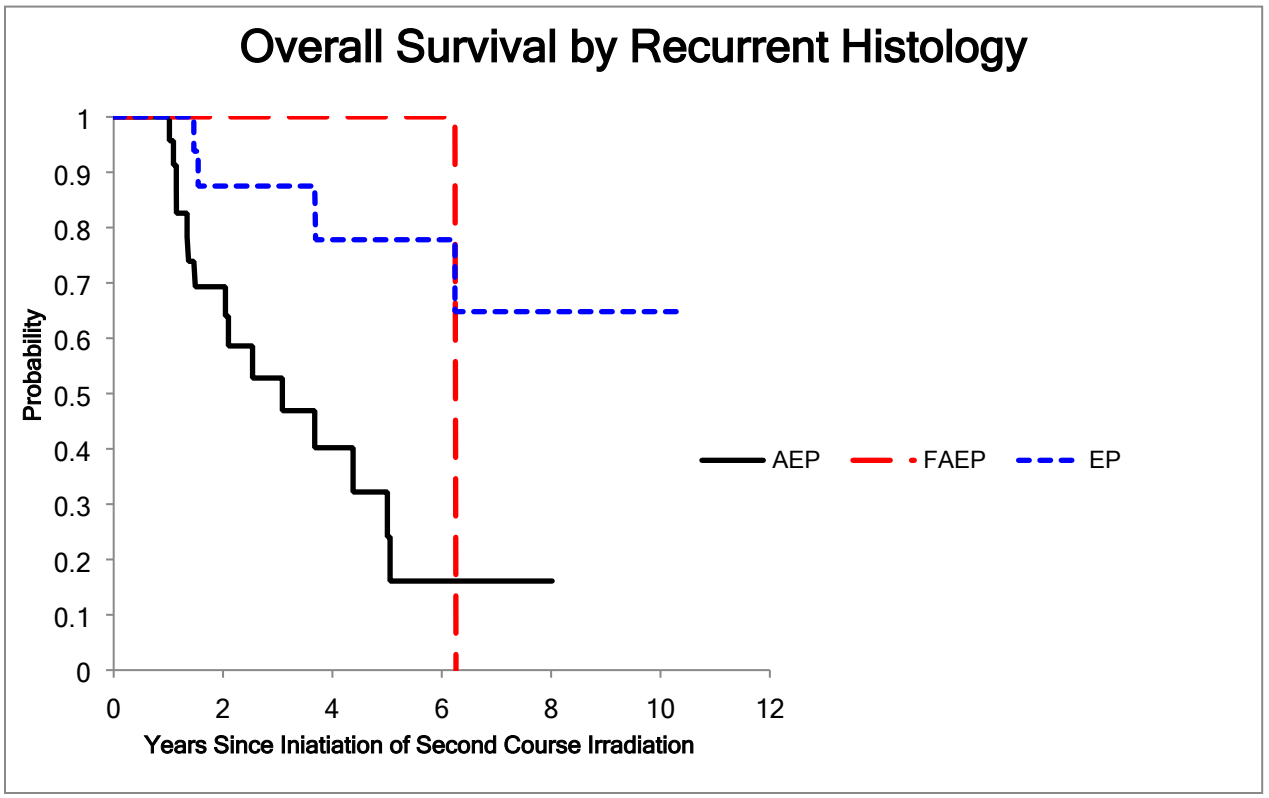
Factors Associated with Outcome: Neuropathology at Initial Recurrence

The following table shows the distribution of neuropathology at initial recurrence, which was not available for 4 of the 50 patients.

Neuropathology at Recurrence		
Anaplastic Ependymoma (AEP)	26	52.0%
Ependymoma (EP)	18	36.0%
Focal Anaplastic Ependymoma (FAEP)	2	4.0%
No Pathology	4	8.00%

Below are Kaplan-Meier estimates of distributions of PFS and OS by recurrent histology. The Cox models following the figures suggest that patients with AEP at recurrence have a worse outcome as measured by PFS and OS.


Progression-Free Survival by Recurrent Histology
Probability
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
12
Years Since Initiation of Second Course of Irradiation
AEP
FAEP
EP


Overall Survival by Recurrent Histology
Probability
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
12
Years Since Iniatiation of Second Course Irradiation
AEP
FAEP
EP

Cox Model of PFS for Recurrent Histology						
	Parameter Estimate	Standard Error	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
AEP vs. (FAEP+ EP)	1.13029	0.42714	0.0081	3.097	1.341	7.153

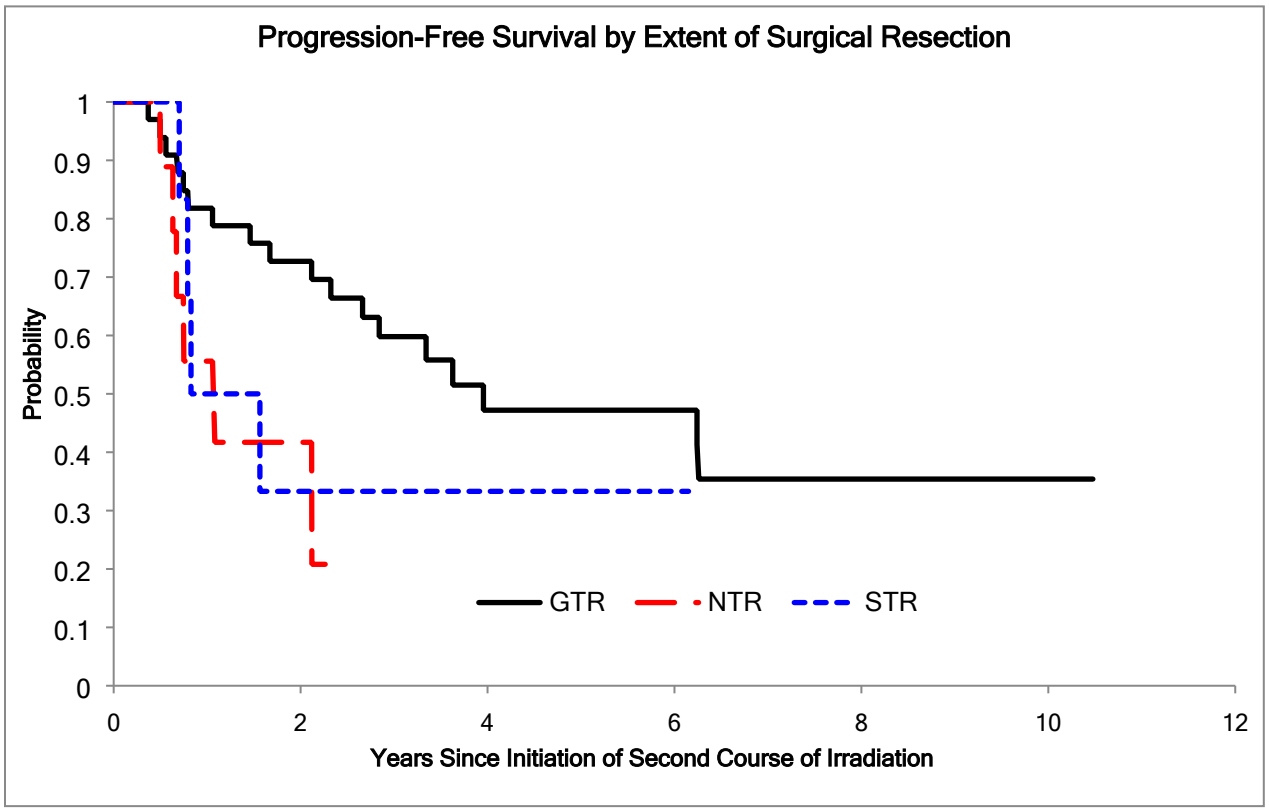
Cox Model of OS for Recurrent Histology						
	Parameter Estimate	Standard Error	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
AEP vs. (FAEP+EP)	1.55020	0.53783	0.0039	4.712	1.642	13.522

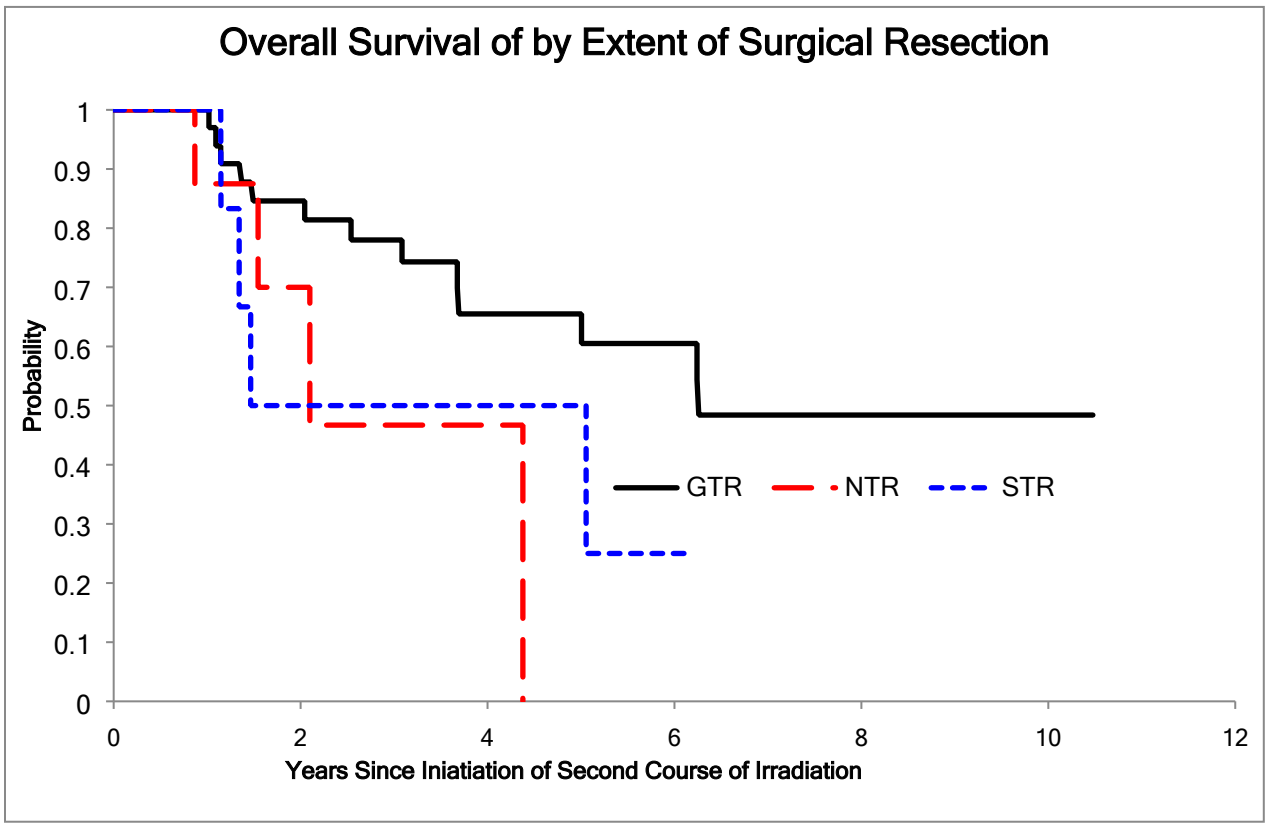
Factors Associated with Outcome: Extent of Surgical Resection at Initial Recurrence

The following table shows the distribution of surgical resection with a gross total resection achieved in 68% of patients.

Extent of Surgical Resection or Metastasectomy		
Gross Total Resection (GTR)	34	68.0%
Near Total Resection (NTR)	9	18.0%
Sub Total Resection (STR)	7	14.0%

Below are Kaplan-Meier estimates of distributions of PFS and OS by extent of surgical resection at initial recurrence. The Cox models following the figures suggest that patients for whom a gross total resection was achieved have better survival.


Progression-Free Survival by Extent of Surgical Resection
Probability
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
12
Years Since Initiation of Second Course of Irradiation
GTR
NTR
STR


Overall Survival of by Extent of Surgical Resection
Probability
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
12
Years Since Iniatiation of Second Course of Irradiation
GTR
NTR
STR

Cox Model of PFS for Extent of Surgical Resection

Neuropathology at Recurrence	Initial Disease Control in Years								Totals	
	≤ 1.22		1.22< - ≤ 1.84		1.84< - ≤ 3.53		3.53< - ≤ 10.35			
	N	%	N	%	N	%	N	%	N	%
AEP	7	26.92	7	26.92	8	30.77	4	15.38	26	52.0
EP	4	22.22	2	11.11	4	22.22	8	44.44	18	36.0
FAEP	0	0	2	100.0	0	0	0	0	2	4.0
No Path	1	25.0	2	50.0	1	25.0	0	0	4	8.0
Totals	12	24.0	13	26.0	13	26.0	12	24.0	50	

	Parameter Estimate	Standard Error	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
GTR vs. NTR +STR	-0.91550	0.42108	0.0297	0.400	0.175	0.914

Cox Model of OS for Extent of Surgical Resection

	Parameter Estimate	Standard Error	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
GTR vs.NTR+STR	-1.01384	0.47177	0.0316	0.363	0.144	0.915

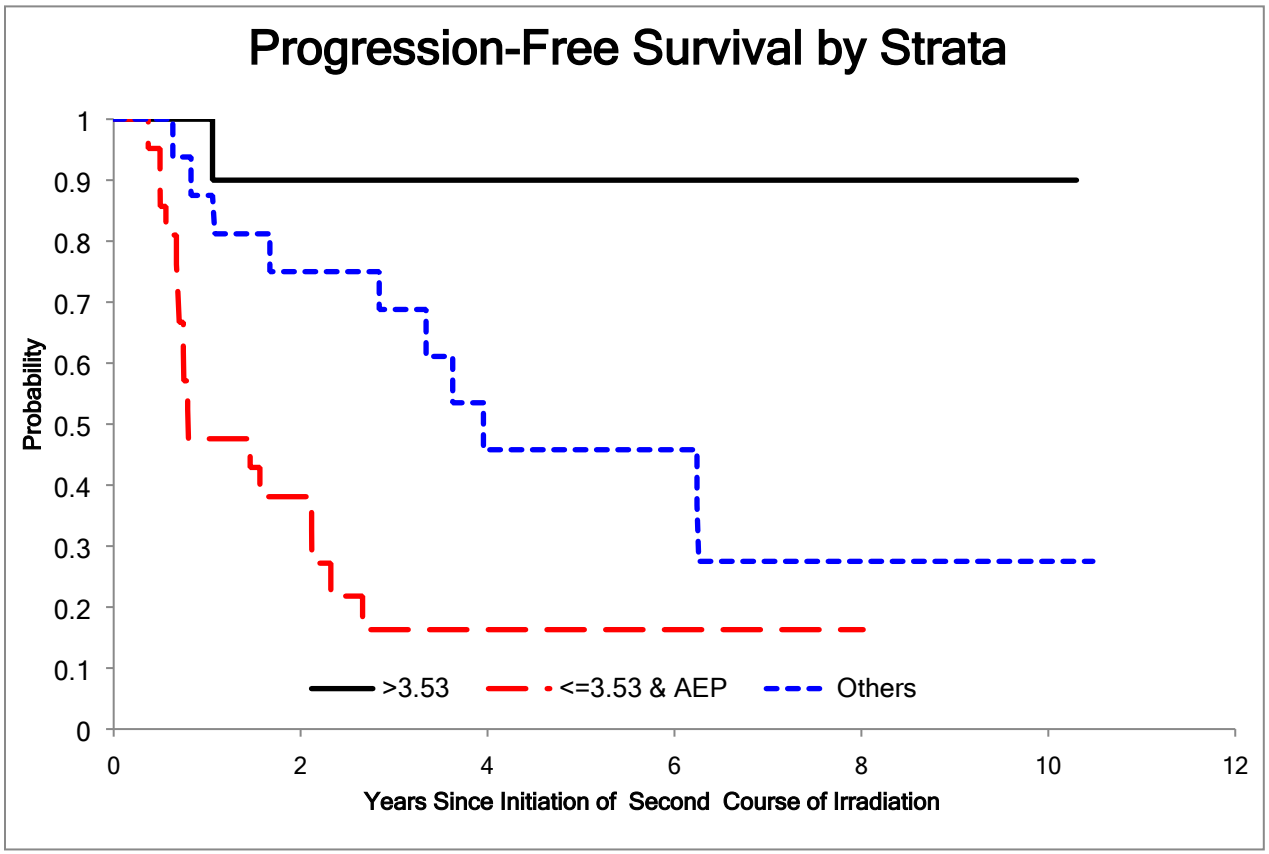
Factors Associated with Outcome: Age at Time of Re-Irradiation

There is no evidence of any association between age at re-irradiation and PFS ($p>0.85$) or OS ($p>0.94$).

Reasonable Prognostic Strata:

The association between duration of initial disease control and neuropathology at recurrence is shown in the following table.

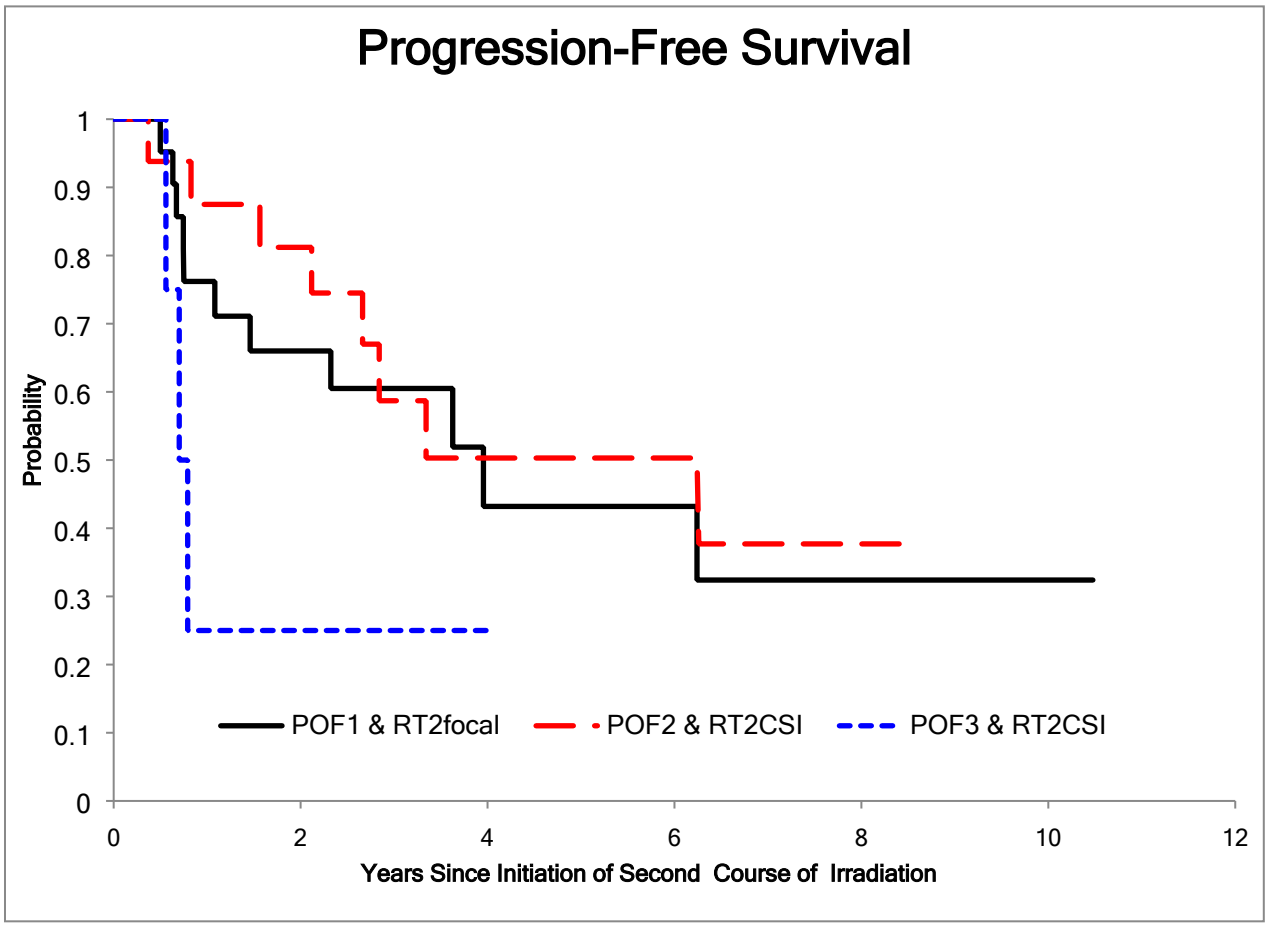
Based on the above analyses of outcome, duration of initial disease control (IDC) longer than 3.53 years identifies a subgroup of approximately 24% of patients with an excellent outcome. Patients who experience shorter durations of initial disease control and have anaplastic ependymoma (AEP) at recurrence identifies a subgroup of approximately 44% of patients with a poor outcome. A third subgroup (Other) of approximately 32% of patients have FAEP or EP or no neuropathology at recurrence and initial disease control less than 3.53 years (<3.53). These three strata are proposed for monitoring PFS for the current trial against the historical data. PFS for the historical cohort by these three strata are shown in the following figure and table. A log-rank comparison of the three groups results in a p-value of 0.0003.



>3.53						*<=3.53 & AEP*					*Others*				
Years Since Initiation of RT2	Risk	Fail	Cens	Prob	SE	Risk	Fail	Cens	Prob	SE	Risk	Fail	Cens	Prob	SE
0	12	0	0	1.000	0.000	22	0	0	1.000	0.000	16	0	0	1.000	0.000
1	12	0	2	1.000	0.000	22	11	1	0.476	0.104	16	2	0	0.875	0.080
2	10	1	1	0.900	0.095	10	2	1	0.381	0.106	14	2	0	0.750	0.104
3	8	0	3	0.900	0.116	7	4	0	0.163	0.075	12	1	1	0.688	0.116
4	5	0	2	0.900	0.142	3	0	0	0.163	0.075	10	3	1	0.458	0.127
5	3	0	0	0.900	0.142	3	0	1	0.163	0.086	6	0	1	0.458	0.138
6	3	0	0	0.900	0.142	2	0	1	0.163	0.106	5	0	0	0.458	0.138
7	3	0	2	0.900	0.201	1	0	0	0.163	0.106	5	2	0	0.275	0.117
8	1	0	0	0.900	0.201	1	0	0	0.163	0.106	3	0	1	0.275	0.135
9	1	0	0	0.900	0.201	1	0	1	0.163	0.149	2	0	1	0.275	0.166
11	1	0	1	0.900	0.285						1	0	1	0.275	0.234

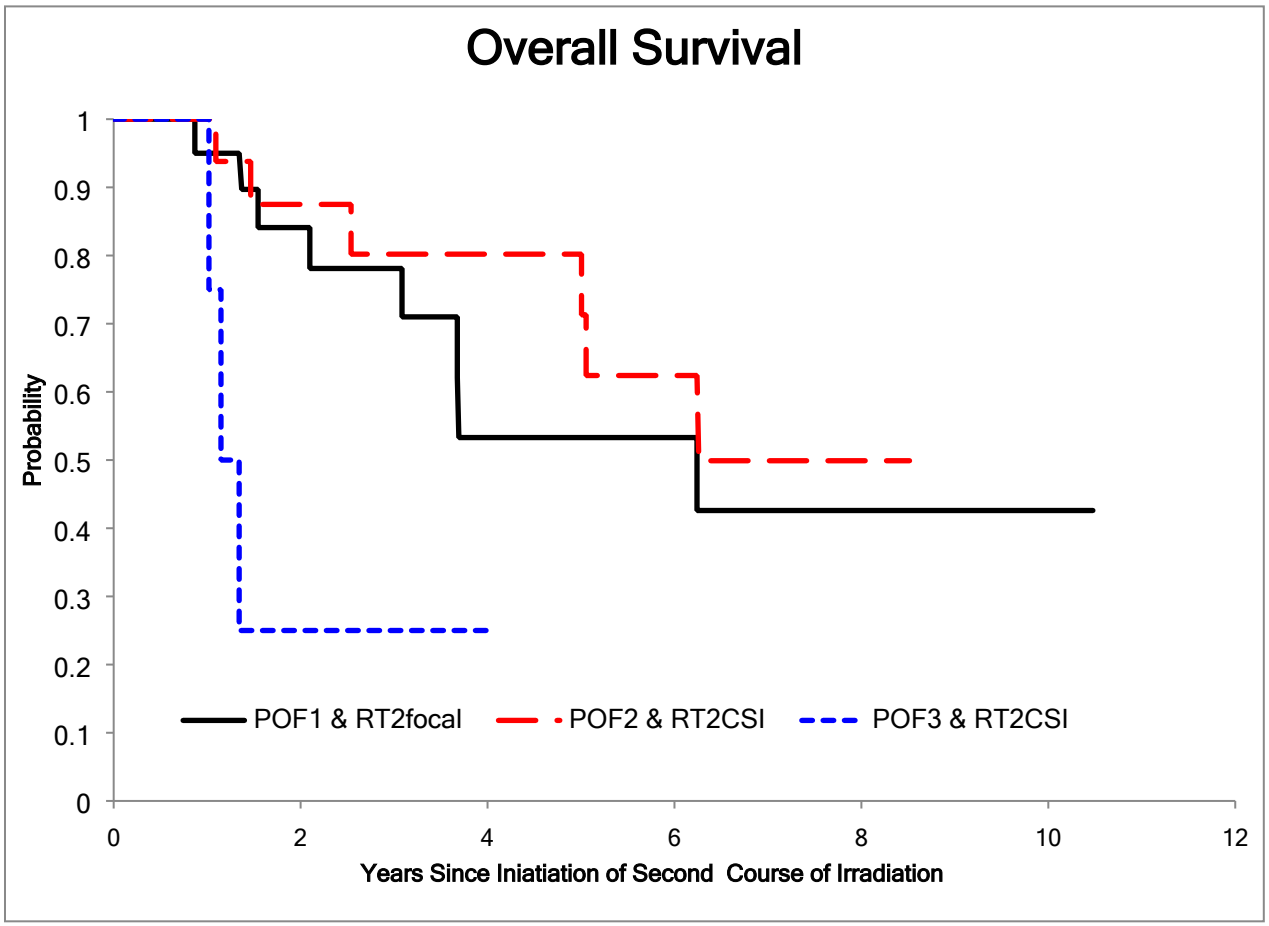
Factors Associated with Outcome: Initial Pattern of Failure and Retreatment Volume

These data are presented to provide evidence for the proposed retreatment volume based on site of tumor recurrence.



Log-rank test: p-value=0.2416

POF1 & RT2focal						***POF2 & RT2CSI***					***POF3 & RT2CSI***				
Years Since Initiation of RT2	Risk	Fail	Cens	Prob	SE	Risk	Fail	Cens	Prob	SE	Risk	Fail	Cens	Prob	SE
0	22	0	0	1.000	0.000	16	0	0	1.000	0.000	5	0	0	1.000	0.000
1	22	5	2	0.762	0.093	16	2	0	0.875	0.080	5	3	1	0.250	0.153
2	15	2	1	0.660	0.107	14	1	1	0.812	0.098	1	0	0	0.250	0.153
3	12	1	2	0.605	0.120	12	3	2	0.587	0.133	1	0	0	0.250	0.153
4	9	2	2	0.432	0.133	7	1	0	0.503	0.134	1	0	0	0.250	0.153
5	5	0	1	0.432	0.146	6	0	0	0.503	0.134	1	0	1	0.250	0.217
6	4	0	0	0.432	0.146	6	0	1	0.503	0.145					
7	4	1	1	0.324	0.154	5	1	1	0.377	0.149					
8	2	0	0	0.324	0.154	3	0	1	0.377	0.172					
9	2	0	0	0.324	0.154	2	0	2	0.377	0.298					
11	2	0	2	0.324	0.267										



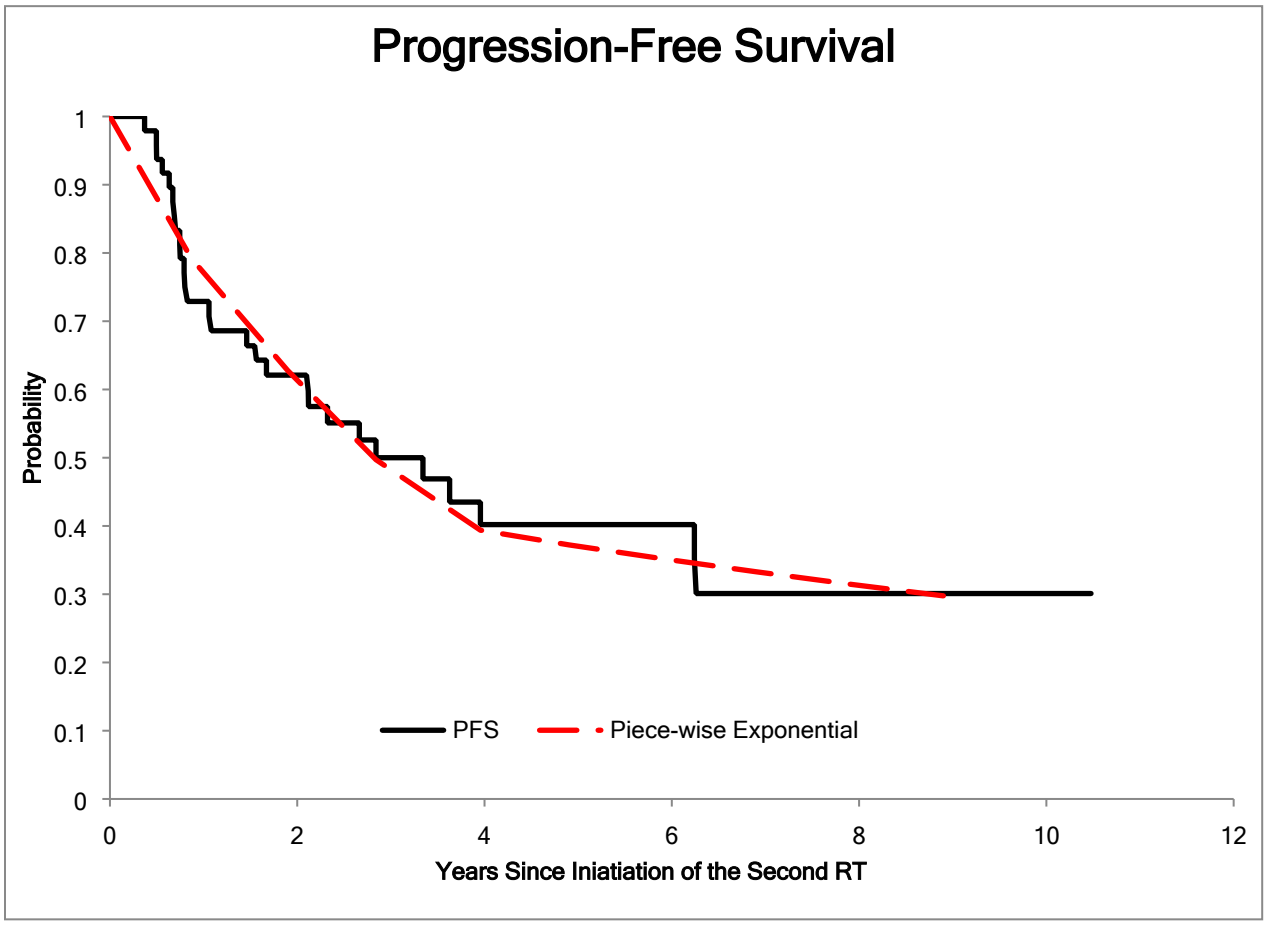
Log-rank test: p-value=0.0242

POF1 & RT2focal						***POF2 & RT2CSI***					***POF3 & RT2CSI***				
Years Since Iniatiation of RT2	Risk	Fail	Cens	Prob	SE	Risk	Fail	Cens	Prob	SE	Risk	Fail	Cens	Prob	SE
0	22	0	0	1.000	0.000	16	0	0	1.000	0.000	5	0	0	1.000	0.000
1	22	1	2	0.950	0.048	16	0	0	1.000	0.000	5	0	1	1.000	0.000
2	19	2	3	0.841	0.087	16	2	1	0.875	0.083	4	3	0	0.250	0.153
3	14	1	2	0.781	0.106	13	1	3	0.802	0.113	1	0	0	0.250	0.153
4	11	3	2	0.533	0.138	9	0	0	0.802	0.113	1	0	0	0.250	0.153
5	6	0	1	0.533	0.149	9	0	0	0.802	0.113	1	0	1	0.250	0.217
6	5	0	0	0.533	0.149	9	2	1	0.624	0.145					
7	5	1	2	0.426	0.186	6	1	2	0.499	0.177					
8	2	0	0	0.426	0.186	3	0	1	0.499	0.204					
9	2	0	0	0.426	0.186	2	0	2	0.499	0.353					
11	2	0	2	0.426	0.323										

11.1 Statistical Analysis of Primary Objective 1.1

The primary objective is to estimate the distributions of PFS and OS post re-irradiation at initial failure for patients with ependymoma. In addition, we will monitor PFS as compared with the retrospective historical data discussed in section 11.0 to ensure that the current approach is not inferior to the retrospective historical experience.

Based on the work of Korn and Freidlin (2006) [297] we will estimate the sample size required to monitor that the prospective results are not inferior to the retrospective results, as if a prospective randomized trial were to be conducted. The historical PFS data were used to estimate the hazard rate during the first 4 years of 0.233 and for the hazard rate for the period greater than 4 years of 0.056. The following figure shows that a piece-wise exponential distribution with these two hazard rates is an outstanding fit to the historical PFS distribution.



The calculations for the monitoring design assume piece-wise exponential distributions. The design will have 80% power to detect an unacceptable decrease in the 3-year PFS rate from 50% to 35% (α=0.10: one-sided test). East© (version 5) was used to calculate that with one interim analysis and approximately 64% of patients assigned to the new treatment, a total of 140 patients would need to be

randomized over 9 years of accrual. Thus, we will need to accrue 90 patients to our new regimen over approximately 9 years. The final analyses will be conducted 2 years after initiation of irradiation for the last patient.

The one interim analysis, based on the work by Xiong et al, [298] will be conducted when 50% of the expected number of failures (67) for the 90 patients to be treated prospectively (assuming the alternative hypothesis) has been observed (~34 patients have failed). The planned interim analysis will occur at approximately 68% of the expected total "transformed information time," assuming the alternative hypothesis. Accrual will be suspended until all available information has been considered, if the observed nominal p-value is ≤0.0582. At the final analysis, one would conclude that the prospective results are inferior to the retrospective results if the p-value is ≤0.10. The log-rank comparisons will be stratified by three strata define above and the power should be retained [299]. With this design the actual significance level is 0.1089; the power is 0.7915 and the maximum probability of an interim decision being discordant with a decision that would be made by a final analysis is 0.05 (5%).

While the expected accrual to this trial is considerably greater than our historical experience, we expect that accruing 12 patients per year is realistic. Our current case review for re-irradiation includes approximately two chart review consultations per month. Patients treated to date include those previously irradiated in department or from our region. Based on institutional policy, patients cannot be accepted for treatment at St. Jude in the absence of a clinical protocol. Thus when this trial opens, we will begin to actively recruit patients for the trial. Furthermore, we have offers from a number of centers to collaborate in this effort. If accrual is not meeting expectations by the end of year 2, we will contact these centers to participate.

At the time of amendment #2, the study had been open for 4 years and we accured 53 patients. The accrual rate was approximately 10 patients/year and less than the 15 patients per year target (initial). We extended the accrual time by 3 years to reach the accrual goal and added a collaborative site.

Stopping Rule for Necrosis:
Necrosis will be monitored throughout the trial and accrual to the trial suspended at any time the following stopping criteria are met. Necrosis will be graded according to the CTCAE v4.0 terminology. If evidence develops that more than 20% of patients are expected to develop necrosis (CTCAE v4.0 > grade 3) the treatment will be considered unacceptable. The number of patients who experience necrosis is based upon the number of enrolled patients. The stopping criteria shown in the following table are based on exact lower 95% Blyth-Still-Casella confidence bounds.

Number of Patients Experiencing Necrosis	Number of Eligible Patients	Exact 95% Lower Confidence Bounds
7	≤ 20	≥ 0.201
10	≤ 30	≥ 0.193
13	≤ 40	≥ 0.204
16	≤ 50	≥ 0.211
18	≤ 60	≥ 0.204
20	≤ 70	≥ 0.202
23	≤ 80	≥ 0.211

11.2 Statistical Analysis of Secondary Objective 1.2.1 Neurological, Endocrine and Cognitive

Objective: To explore potential associations of clinical and treatment factors with the incidence and severity of neurological, endocrine and cognitive deficits in children and young adults with ependymoma treated with a second course of irradiation.

To assess the side effects of radiation therapy in neurology, ophthalmology, audiology, endocrinology, and cognitive state, the data will be collected in a longitudinal setting. The time schedule for data collection is presented in Table 6.0.1 (Evaluations at baseline and follow-up). Since patients treated by focal or craniospinal radiation will be not at random, to compare the treatment effect, we need to adjust other clinical factors to limit the confound effects in the regression models as discuss below. In addition to the analysis plan below, once we have 15 patients in each stratum (a total of at least 45 patients) followed for 1 year, descriptive statistical analyses and regression analyses as discussed below will be conducted. The results of these interim analyses will be submitted for presentation at an appropriate national scientific meeting, as well as to the CT-SRC. There are not expectations that the findings of these interim analyses would raise concerns for the current trial.

Neurology: The neurologic signs and symptoms such as seizures, headache, motor sensation, ataxia, cranial nerve deficits and others will be collected. Neurological data will be obtained from the neurological protocol exam form. Grade 3-5 toxicity data as determined by the NCI CTCAE v 4.0 will be reported. The distribution of ordinal outcomes and percentages will be estimated. Mixed-effects Proportional Odds Regression [300] will be performed to estimate their changes over time, and compare severity in the two treatment arms adjusted by confound factors.

Ophthalmology: Vision status of a patient will be dichotomized into None and Impaired, according to clinical meanings, as described in Section 6.3. We will

also use the information recorded in the clinical neurology form (see appendix) and NCI CTCAE v4.0 when relevant. The percentages for both statuses will be estimated. Generalized Estimating Equations (GEE) with logistic link will be employed to estimate the change of vision over time, and compare severity of vision in the two treatment groups adjusted by confound factors.

Audiology: To assess hearing loss in patients, hearing will be dichotomized as normal if all thresholds are within 0-20 DB HL and otherwise abnormal. GEE with logistic link will be modeled to explore the trend over time and investigate impacts of specific clinical and treatment factors on hearing loss. In the presence of missing data, Weighted GEE will be employed to address missingness. In addition, the cumulative incidence of hearing loss will be estimated with death as a competing risk. Chang Ototoxicity Grading Scale (COGS) will also be used to evaluate the hearing loss. The ordinal COGS will be analyzed similarly as Neurology grade.

Endocrine: Endocrine data as a continuous variable will be collected. Descriptive statistical analysis will be performed. Diabetes Insipidus (DI) is a hormone deficiency that results only from direct damage to the hypothalamus and pituitary axis (mainly pituitary stalk) by tumor or surgery. This longitudinal binary variable (coded as “yes” or “no”) will be compared between the surgery and radiation groups using GEE adjusted by other confounding factors. Hormone Deficiency, such as Growth Hormone Deficiency (GHD), will be compared between the surgery and radiation groups. Growth hormone will be dichotomized with GHD=1 for <7ng/ml and GHD=0, otherwise. We define GHD=1 as event. Since the treatment of other hormone deficiency could be a compete risk for this event, cumulative incidence regression analysis using Fine and Gary method will be employed [301]. Specific clinical and treatment group factors will be included as covariates to investigate the treatment group difference. Other Hormone Deficiency, including Thyroid Hormone Deficiency (central hypothyroidism), Adrenal Insufficiency, Gonadotropin Deficiency or Precocious Puberty, Diabetes Insipidus, Hypothalamic Obesity (not a specific endocrine deficiency but an endocrine problem nonetheless), will be analyzed similarly. Some of these measures are graded in the NCI CTCAE v4.0.

Neurocognitive: Neurocognitive measures are continuous. GEE will be employed to estimate treatment group difference with specific clinical factors and time also included as covariates. For some neurocognitive measures, children and young adults (adolescents) will have different forms. When we pool data together to perform the analysis, we will take these differences into account in the GEE model to control for variations. Neurocognitive measures will also be dichotomized into normal and abnormal groups based on cut-off values (average range vs. outside of the average range for a given test instrument) at specific time points after therapy. GEE with logistic link will be used to investigate the treatment group effect. Frequency and percentage of dichotomized cognitive measures will be calculated.

11.3 Statistical Analysis of Secondary Objective 1.2.2 Sleep, Fatigue and Quality of Life

Objective: Using specific measures of sleep quality, excessive daytime sleepiness, daytime activity, fatigue, symptom distress, and quality of life, explore associations of sleep, fatigue and quality of life with other measures of CNS effects, clinical and treatment factors in children and young adults with ependymoma treated with a second course of irradiation.

Stratified by treatment arms (focal vs. craniospinal radiation), descriptive statistics of the longitudinal assessments of sleep, fatigue and quality of life will be described. Specifically, on a yearly basis starting from the pre-treatment time point to year 5 post treatment initiation, quality of life in patients ≥ 2 years of age as measured by the PedsQoL brain tumor module will be reported; daytime activity and up to 20 sleep measurements as measured by wrist actigraphy along with sleep diary-patient/parent will be reported. On a more frequent basis (every 3 months for the first 2 years, every 6 month to month 60), sleep complaints in patients ≥ 8 years of age as measured by Symptom Distress Scale (SDS) and Epworth Sleepiness Scale will be reported and fatigue in patients ≥ 2 years of age as measured by The Peds QL Multidimensional Fatigue scale will be reported, along with PedsQoL brain tumor module. The Acute version of the Multidimensional Fatigue scale and Peds brain tumor module will be administered weekly during radiation therapy.

As an exploratory analysis, each of above mentioned measurements will be compared between two treatment arms by longitudinal data analysis. Generalized Estimating Equation (GEE) will be employed to compare outcome changes over time between two treatment arms by using time and treatment as covariates of the model. The interaction term between treatment arm and time will be added if two arms show different change rate. The other covariates of interest will be selected by Bayesian information criterion (BIC). However, any response with <3 assessments would not be included in the list. To analyze sleep measurements which will be examined annually, the other measurements used in the model will only include their data points measured at the same time as sleep measurements. Multidimensional Fatigue scale and Peds brain tumor module will be measured each week for 4 weeks at the first year. We will analyze them in two ways. First, we will only use the first 4 weeks data to fit the GEE. Second, it will also be fitted in a large time picture but only the first week data of these 4 weeks will be used. In addition, Epworth Sleepiness Scale score will also be dichotomized by 10 and then fitted using GEE with a logistic link.

Similarly, the same modeling approach will be used to explore associations between each of above mentioned outcome and patient characteristics/clinical

factors that are of interest. The independent effect of resultant significant factors will be explored further in multiple regression models.

Based on the number of tests performed to address this secondary objective, adjustments for multiple comparisons will be made to mitigate over interpreting exploratory findings.

11.4 Statistical Analysis of Secondary Objective 1.2.3 Physical Performance

Objective: To describe physical performance and movement in children, adolescents and young adults with ependymoma treated with a second course of radiation.

Physical performance measures will be obtained at baseline, 12, 24, 36, 48 and 60 months. We will provide descriptive statistics of the following outcomes at each time point, and also provide the plots of individual profiles and mean profiles of the outcomes across time. The descriptive statistical analysis will be stratified by gender, age at diagnosis and total dose of brain radiation.

To model the outcomes' pattern and change over time, we will use generalized estimating equation (GEE) methodology with time as the main independent variable while adjusting for gender, age at diagnosis and total dose of brain radiation, including an interaction term if indicated. The assigned distribution and link function in each model will depend on the characteristic of the specific outcome as listed in next paragraph(s). The continuous measures will be modeled using normal distribution and identity link whereas the binary outcomes will be modeled using binomial distribution and logit link.

These analyses will be conducted at the conclusion of the trial and at an interim time point at which we have 15 patients in each stratum (a total of at least 45 patients) followed for 1 year. The results of the interim analyses will be submitted for presentation at an appropriate national scientific meeting, as well as to the CT-SRC.

List of outcomes:

1. Overall physical performance: Two sets.
   (a) Measured task sets: BOT2 (4-21 years old) and PPT (≥22 years old).
      - BOT2 outcome: total motor composite, a standardized score range from 20 to 80, with a mean of 50 and a standard deviation of 10.
      - PPT (7-item questionnaire) outcome: a score range from 0 to 28. The normative data is available from the human performance lab.

We will standardize the two above scores into z-scores for data analysis.

(b) Self-reported instruments (PROMIS): Three questionnaires.
- Pediatric Physical Function – Mobility – SF1: 8-item questionnaire with the score range from 0 to 32.
- Pediatric Physical Function – Upper Extremity – SF1: same as above.
- Physical Function – SF1: 10-item questionnaire with the score range from 0 to 50.

We will standardize the above scores into T-scores for data analysis based on the normative data from PROMIS.

2. Body Composition: BMI (kg/m2) and waist/hip ratio (cm/cm).
3. Flexibility
   (a) Ankle dorsiflexion active and passive range of motion: measured by goniometer, and recorded as an angle (degree).
   (b) Overall flexibility: measured by sit and reach test, and recorded as a length (cm).
4. Balance

Measured by sensory organization test (SOT), and the result from the test is the equilibrium score, a percentage range from 0% to 100%, with the higher percentage, the better balance. The outcome is a binary variable with a cutoff score of < 70% indicates future risk for a fall.

5. Coordination
   (a) Fine motor coordination (finger and hand coordination). Measured by Composite Cerebellar Functional Severity Score (CCFS), and the outcome is an age-adjusted z-score and log transformed.

   (b) Overall coordination
   Measure by brief ataxia rating scale (five-item questionnaire). The outcome is a total scale range from 0 to 22.

6. Muscle strength and power
   (a) Lower extremity strength: measured by BiodexIII, and the outcomes are peak torque value/body weight ratios at different speeds of motion.
   (b) Hand grip strength: measured by a Jamar hand held dynamometer and recorded in kilograms (kg).

We will standardize the above scores into z-scores for data analysis based on normative data.

7. Cardiopulmonary fitness

(a) Resting Energy Expenditure: measured with indirect calorimetry after an overnight fast and recorded as REE (kcal/day).
(b) Cardiopulmonary Exercise test (CPET): the test will be completed on a treadmill using the Balke protocol or cycle ergometer using an incremental ramping protocol. The outcome is recorded as VO2max (ml/kg/min).

We will standardize the above scores into z-scores for data analysis based on normative data.

11.5 Statistical Analysis of Secondary Objective 1.2.4 Neuroimaging

Objective: Estimate and compare the response of residual tumor and the incidence and severity of structural, functional and vascular effects of normal brain in children and young adults with ependymoma after treatment with a second course of irradiation using specific methods of diffusion, contrast-enhancement, vascular and functional neuroimaging, and explore the association between these and other measures of CNS effects and clinical and treatment factors. Determine the time course of white matter tract injury and recovery post irradiation and the association between imaging metrics derived from serial quantitative neural imaging and radiation dosimetry as well as neuro-cognitive outcomes.

Mixed effect models will be used to estimate and compare the structural, functional and vascular effects over time of normal brain and residual tumor in children and young adults with ependymoma after treatment with a second course of irradiation based on comprehensive imaging from MTR, DTI, DSC and SWI etc. Associations of those changes in the brain with other measures of CNS effects and clinical and treatment factors will be investigated using mixed effects models as well. The time course of white matter tract injury and recovery post irradiation by MTR and DTI will be described graphically and fitted by mixed effect models. The association between those quantitative neural imaging measurements change and radiation dosimetry/neuro-cognitive outcomes will be explored by mixed effect models.

Based on the number of tests performed to address this secondary objective, adjustments for multiple comparisons will be made to mitigate over interpreting exploratory findings. After the acquisition of four DTI/MT examinations in 15 patients in each stratum (a total of at least 45 examinations), interim analysis of MT imaging data will be performed and reported at an appropriate scientific meeting, as well as to the CT-SRC. The investigational MT sequence will no longer be performed after 8/1/2020.

11.6 Statistical Analysis of Exploratory Objective 1.3.1 Avidity to FDG and C-MET

Objective: Estimate the avidity of ependymoma to ^{18}F-fluorodeoxyglucose (FDG) and ^{11}C-methionine positron emission tomography (IND # 104987) prior to

radiation therapy and correlate change in avidity 12, 24 and 36 months after a second course of irradiation with tumor progression. Estimate the avidity of FDG-PET and MET-PET at baseline and compare those two by t test or Wilcoxon rank sum test based on the distribution of the variables. The association between tumor progression and avidity to FDG and to MET will be explored by Cox regression model by using PFS as response variable and avidity measurements as time dependent covariates, where clinical and demographics variables of interest may also be included in these models, if the number of events is sufficient to support such a multivariable analysis. The association between PFS and baseline avidity will be also investigated. In these survival models, nine events per covariate are required. We will describe necrosis based on MET/FDG descriptively and graphically. The association between necrosis findings based on MET/FDG and necrosis findings based on MRI will be explored by mixed effect model.

Based on the number of tests performed to address this secondary objective, adjustments for multiple comparisons will be made to mitigate over interpreting exploratory findings.

11.7 Statistical Analysis of Exploratory Objective 1.3.2 Growth Factor and Cytokine Responses

Objective: Measure growth factor and cytokine responses in children and young adults with recurrent ependymoma after treatment with a second course of irradiation, and explore associations between these and other measures of CNS effects and clinical and treatment factors.

Growth factor and cytokine responses in serum will be measured longitudinally before, during and post radiation therapy in consenting patients. Hence the planned exploratory analyses based on this data will mainly utilize longitudinal models. We will study possible associations between cytokine levels and demographic and clinical variables, response to treatment as measured by PFS as well as between cytokine levels and various side effects. We will investigate possible associations between the change in cytokine levels and factors such as radiation dose and irradiated volume, tumor volume, tumor response, surgical and host factors, etc. We will also evaluate presence of associations between cytokine responses and measures of sleep, fatigue and function as well as associations between cytokine responses and neurological, endocrine and cognitive/quality of life parameters. Additionally, we will examine whether an association exists between dose distribution and cytokine response. Considering the large number of exploratory analyses planned for these data, the multiplicity issues that will arise will be addressed by reporting false discovery rate estimates.

11.8 Statistical Analysis of Exploratory Objective 1.3.3 Radiogenomics

Objective: Conduct a variety of exploratory genetic analyses on tumor samples (and blood where a germline control is required), including but not limited to

broad (genome-wide/array based) or focused (gene-specific) analyses at the DNA, RNA, or protein level and next generation sequencing in an effort to better understand the biology of ependymoma. Explore associations between molecular findings and treatment response and various side effects including vasculopathy, hearing loss, cognitive deficits, and growth hormone deficiency and other measures as appropriate.

This objective carries a general goal of exploring the genetic basis of ependymoma in an effort to identify genetic variations which may associate with tumor formation, treatment responses and toxicity. We will use statistical association tests, as appropriate, to investigate the association between genotypes and these phenotypes of interest. We will compare sequence/genetic variations from germline, untreated tumor and treated tumor samples to pinpoint the genetic events occurring during tumor initiation and development. Considering the large number of exploratory analyses planned for these data, the multiplicity issues that will arise will be addressed by reporting false discovery rate estimates.

A important goal of this analysis is to identify genetic variations in germline that predict for side effects from RT with the long-term aim of screening susceptible patients prior to irradiation and to study the biology of late effect. We will investigate genetic variants associated with side effects related phenotypes: vasculopathy, hearing loss, cognitive deficiencies, and hormone deficiencies by genome-wide association studies and candidate gene analyses. The currently known candidate genes and gene mutations for the phenotypes of interest are described below. However, since these data won't be available for several years from the initiation of enrollment and in some cases later if longer term follow-up is needed, the list of candidate genes may change substantially by the time we are ready to perform these analyses. Hence, the analysis plan below merely reflects the current state of knowledge and is subject to change.

Genetic Abnormalities Associated with Vasculopathy: The candidate genes based on current knowledge include: 1) gene HgS, IL4R, TNF, ADRB, VCAM-1 and LDLR which were associated with stroke risk in sickle cell disease (SCD) patients; 2) gene Factor II, Factor V, MTHFR and PAI-1 and promoter region of GPx-3 gene which were associated with venous sinus thrombosis and arterial ischemic stroke; 3) gene ELNINT20/INT23, COL1A2 and TNFRSF13B which were associated with intracranial aneurysm (IA) risk; 4) inositol 1,4,5-triphosphate 3-kinase C (ITPKC) gene which were associated with Kawasaki disease susceptibility and formation of coronary artery aneurisms; 5) HLA-AW24, -BW46, and -BW54 serotypes which are associated with Moya-moya syndrome, defined as bilateral severe stenosis or occlusion of the internal carotid arteries with collateral formation.

Genetic Abnormalities Associated with Hearing Loss: The candidate gene mutations under our investigation include: 1) mutations of the GJB2 gene which was associated with recessive and sporadic deafness; 2) mutations in the

mitochondrial 12S ribosomal RNA gene which were associated with ototoxicity for patients taken Aminoglycoside antibiotics; 3) GSTP1 gene and megalin mutations which were associated with cisplatin-induced ototoxicity.

Genetic Abnormalities Associated with Cognitive Deficiencies: The candidate genes under our investigation include: 1) GDI1, oligophrenin, PAK3, FMR2, IL1RAPL, TM4SF2, VCX-A, ARHGEF6, GPC3, GPC4 and HTR2A which were associated with nonsyndromic mental retardation (NSMR); 2) SNAP-25 gene and APOE gene which were associated with cognitive function; 3) 894TT genotype of NOS3 gene which was associated with cognitive decline following radiation therapy; 4) COMT genotype which was associated with white matter performance and resiliency against late effects of irradiation.

Genetic Abnormalities Associated with Hormone Deficiencies: The candidate genes under our investigation include: genetic aberrations in GST (GSTM1, GSTP1, GSTT1) which have been associated with the risk of relapse of certain cancers and modulate response to therapy; GSTM1 gene was associated with susceptibility to growth hormone deficiency.

11.9 Statistical Analyses of Exploratory Objective 1.3.4: Association of prior chemotherapy with PFS and OS distributions.

Cox proportional hazard models will be used to explore possible association of chemotherapy given prior to re-irradiation with outcome. Due to the expected limited sample sizes for any chemotherapy agent, the results of these exploratory analyses will be considered as descriptive.

11.10 Statistical Analyses of Exploratory Objective 1.3.5: To compare the progression-free and overall survival distributions for children (age > 3 years) and young adults with recurrent ependymoma and 1q gain treated with a second course of irradiation (focal or craniospinal) while monitoring for excessive central nervous system necrosis.

Of the 117 patients in RT1 cohort, total of 20 had a “distant or combined” pattern of failure, 8 did and 12 did not have 1q gain. Total of 22 patients had a “local” pattern of failure, 4 did and 18 did not have 1q gain. A total of 75 patients did not experience treatment failure (tumor progression), 4 did and 71 did not have 1q gain. The detailed frequency is shown in Table 1. There is association between type of failure with 1q gain status (p=0.0003, Chi-square test).

Table 1. Pattern of failure by 1q gain status

Pattern of Failure	1q gain		
	No	Yes	Total
Distant or Combined	12	8	20
Local Only	18	4	22
None	71	4	75

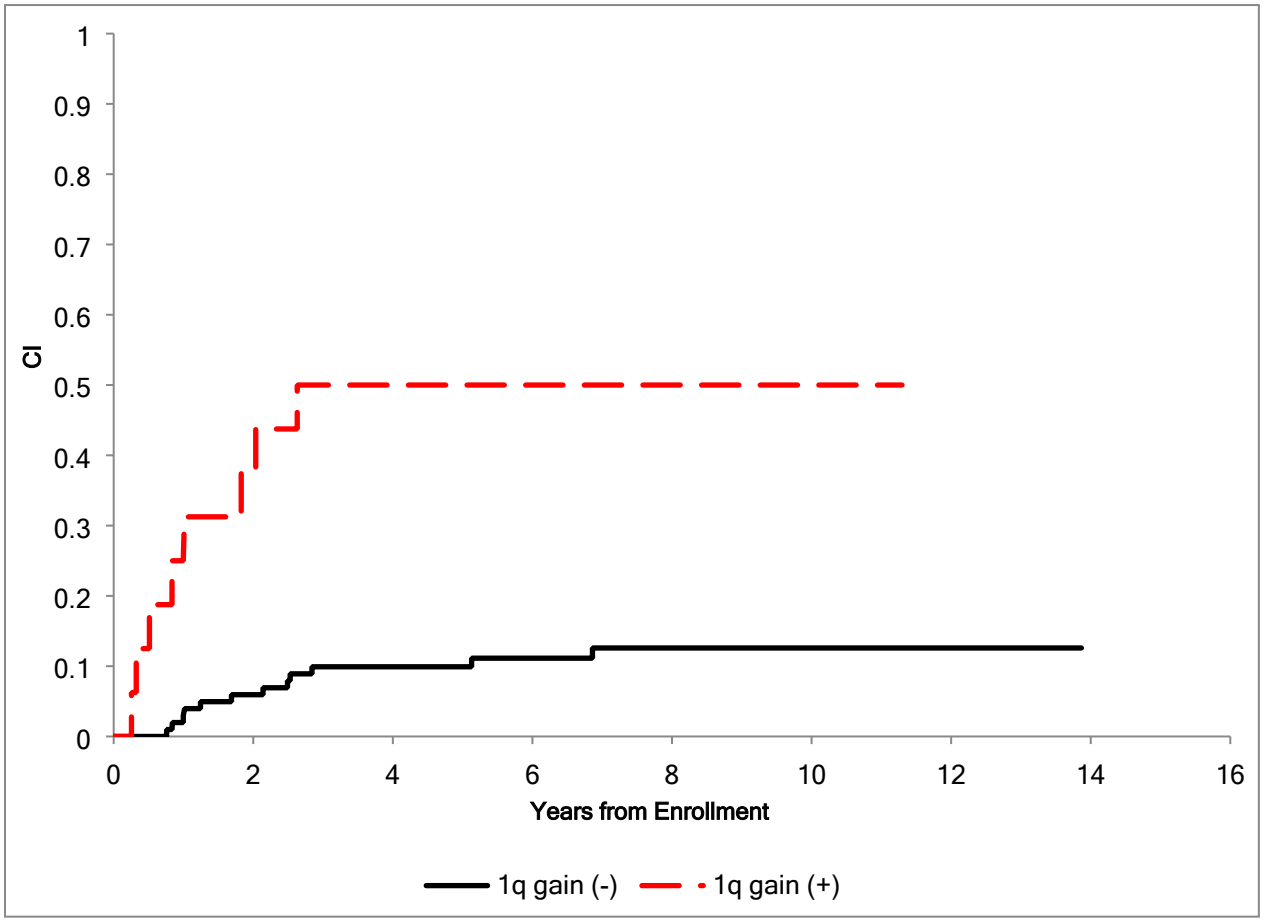
Total	101	16	117

Cumulative incidence of Distant or combined failure by 1q gain status
The cumulative incidence of distant or combined failure analysis with competing risks was assessed. The distant or combined failure was considered as event and other events (local failure and death) were considered as competing risks. Patients with no events were considered as censored. The cumulative incidence with competing risks is shown in Table 2 and plotted in Figure 1. The cumulative incidence of distant or combined failure after 14 years of follow-up was 0.1256 ± 0.0346 (Table 2) for patients without 1q gain, considering the competing risk factors. The cumulative incidence of distant or combined failure after 12 years of follow-up was 0.5000 ± 0.1328 for patients with 1q gain, considering the competing risk factors. The Chi-square test had P value of <0.0001 (Table 2), indicating that there was statistically significant difference for the cumulative incidence of distant or combined failure among patients with the presence of 1q gain vs. absence of 1q gain.

Table 2. Cumulative incidence of distant or combined failure for infratentorial ependymoma patients with competing risks Chi-square = 15.8814, df = 1, p = 0.0000674383

no_Gain_1q							***Gain_1q***						
Years since start of RT	Risk	Fail	Fail other	Cens	CI	SE	Years since start of RT	Risk	Fail	Fail other	Cens	CI	SE
0	101	0	0	0	0.0000	0.0000	0	16	0	0	0	0.0000	0.0000
1	101	3	3	0	0.0297	0.0170	1	16	4	1	0	0.2500	0.1123
2	95	3	6	0	0.0594	0.0236	2	11	2	2	0	0.3750	0.1267
3	86	4	7	2	0.0991	0.0299	3	7	2	0	0	0.5000	0.1328
4	73	0	2	2	0.0991	0.0299	4	5	0	0	0	0.5000	0.1328
5	69	0	0	8	0.0991	0.0299	5	5	0	0	1	0.5000	0.1328
6	61	1	1	4	0.1114	0.0320	6	4	0	0	1	0.5000	0.1328
7	55	1	1	8	0.1259	0.0346	7	3	0	1	0	0.5000	0.1328
8	45	0	0	7	0.1259	0.0346	8	2	0	0	0	0.5000	0.1328
9	38	0	2	6	0.1259	0.0346	9	2	0	0	0	0.5000	0.1328
10	30	0	1	5	0.1259	0.0346	10	2	0	0	1	0.5000	0.1328
11	24	0	0	11	0.1259	0.0346	11	1	0	0	0	0.5000	0.1328
12	13	0	0	6	0.1259	0.0346	12	1	0	0	1	0.5000	0.1328
13	7	0	0	6	0.1259	0.0346							
14	1	0	0	1	0.1259	0.0346							

Figure 1: Cumulative Incidence of Distant or Combined Failure for RT1 Patients with Competing Risks



So, the 1q gain status is important factor to consider when plan treatment of cranial spinal irradiation vs. focal irradiation by historic data. We will offer patients the optional second course of cranial spinal irradiation treatment when they have 1q gain in this procol. We will compare PFS and OS of patients with 1q gain status who receive cranial spinal irradiation vs. focal irradiation by log rank test if sample size is reasonable big. Due to the expected limited sample sizes, the results of these exploratory analyses will be considered as descriptive.

11.11 Monitoring Outcomes for the Retrospective Cohort

The primary objective of this study is to estimate the distributions of PFS and OS after re-irradiation for patients with ependymoma and comparing them to retrospective historical data. Because of the clinicopathologic factors that predict for disease control and functional outcomes and clinical and treatment factors associated with complications evolve over time and will affect the analyses performed for patients enrolled on this study, we will periodically update outcomes from our retrospective cohort to be published and used for comparative analysis. This means that RERTEP will include a retrospective assessment of

disease control and functional outcomes for re-irradiated ependymoma patients treated prior to the activation of this study or those not enrolled. The retrospective review will include an update of the PFS and OS analyses used to develop the statistical design for this study, limited functional outcome and complication assessments used to design the secondary and exploratory aims, incorporate and updating clinicopathologic assessments routinely performed for patients with ependymoma, and other clinical and treatment factors and measures of CNS effects. The list of patients to whom this retrospective research applies will be available through protocol documents in TRACKS.

12.0 OBTAINING INFORMED CONSENT

12.1 Consent/Assent at Enrollment

The process of obtaining informed consent will follow institutional guidelines. Informed consent will be obtained by the attending physician or their designee after the diagnosis of recurrent ependymoma is confirmed and the research participant is deemed eligible. We will seek consent from parents or guardians if the research participant is less than 18 year old and from the research participant if he/she is 18 years of age or older. Verbal assent will be obtained from research participants 7 to 14 years of age and written assent from research participants 14 to less than 18 years of age. A copy of the signed document will be given to the person who has signed the form.

12.2 Consent at Age of Majority

When a participant who was enrolled in the study with parental or guardian permission subsequently reaches the age of majority (18 years of age), the participant must go through an informed consent process in order to continue participation in the study.

13.0 REFERENCES

References

[1] Bauman GS, Sneed PK, Wara WM, Stalpers LJ, Chang SM, McDermott MW, et al. Reirradiation of primary CNS tumors. Int J Radiat Oncol Biol Phys. 1996;36:433-41.

[2] Milker-Zabel S, Zabel A, Thilmann C, Schlegel W, Wannenmacher M, Debus J. Clinical results of retreatment of vertebral bone metastases by stereotactic conformal radiotherapy and intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys. 2003;55:162-7.

[3] Lo SS, Chang EL, Sloan AE. Role of stereotactic radiosurgery and fractionated stereotactic radiotherapy in the management of intracranial ependymoma. Expert Rev Neurother. 2006;6:501-7.

[4] Weprin BE, Hall WA, Cho KH, Sperduto PW, Gerbi BJ, Moertel C. Stereotactic radiosurgery in pediatric patients. Pediatr Neurol. 1996;15:193-9.

[5] Bouffet E, Hawkins CE, Ballourah W, Taylor MD, Bartels UK, Schoenhoff N, et al. Survival benefit for pediatric patients with recurrent ependymoma treated with reirradiation. Int J Radiat Oncol Biol Phys. 2012;83:1541-8.

[6] Merchant TE, Li C, Xiong X, Kun LE, Boop FA, Sanford RA. Conformal radiotherapy after surgery for paediatric ependymoma: a prospective study. Lancet Oncol. 2009;10:258-66.

[7] Merchant TE. Three-dimensional conformal radiation therapy for ependymoma. Childs Nerv Syst. 2009;25:1261-8.

[8] Nieder C, Milas L, Ang KK. Tissue tolerance to reirradiation. Semin Radiat Oncol. 2000;10:200-9.

[9] Nieder C, Grosu AL, Andratschke NH, Molls M. Update of human spinal cord reirradiation tolerance based on additional data from 38 patients. Int J Radiat Oncol Biol Phys. 2006;66:1446-9.

[10] Sminia P, van der Kleij AJ, Carl UM, Feldmeier JJ, Hartmann KA. Prophylactic hyperbaric oxygen treatment and rat spinal cord re-irradiation. Cancer Lett. 2003;191:59-65.

[11] Dritschilo A, Bruckman JE, Cassady JR, Belli JA. Tolerance of brain to multiple courses of radiation therapy. I. Clinical experiences. Br J Radiol. 1981;54:782-6.

[12] Arcicasa M, Roncadin M, Bidoli E, Dedkov A, Gigante M, Trovo MG. Reirradiation and lomustine in patients with relapsed high-grade gliomas. Int J Radiat Oncol Biol Phys. 1999;43:789-93.

[13] Kim HK, Thornton AF, Greenberg HS, Page MA, Junck L, Sandler HM. Results of re-irradiation of primary intracranial neoplasms with three-dimensional conformal therapy. Am J Clin Oncol. 1997;20:358-63.

[14] Combs SE, Ahmadi R, Schulz-Ertner D, Thilmann C, Debus J. Recurrent low-grade gliomas: the role of fractionated stereotactic re-irradiation. J Neurooncol. 2005;71:319-23.

[15] Combs SE, Gutwein S, Thilmann C, Huber P, Debus J, Schulz-Ertner D. Stereotactically guided fractionated re-irradiation in recurrent glioblastoma multiforme. J Neurooncol. 2005;74:167-71.

[16] Combs SE, Thilmann C, Debus J, Schulz-Ertner D. Local radiotherapeutic management of ependymomas with fractionated stereotactic radiotherapy (FSRT). BMC Cancer. 2006;6:222.

[17] Merchant TE, Boop FA, Kun LE, Sanford RA. A retrospective study of surgery and reirradiation for recurrent ependymoma. Int J Radiat Oncol Biol Phys. 2008;71:87-97.

[18] Morris EB, Li C, Khan RB, Sanford RA, Boop F, Pinlac R, et al. Evolution of neurological impairment in pediatric infratentorial ependymoma patients. J Neurooncol. 2009;94:391-8.

[19] Merchant TE. Current management of childhood ependymoma. Oncology (Williston Park). 2002;16:629-42, 44.

[20] Grill J, Renaux VK, Bulteau C, Viguier D, Levy-Piebois C, Sainte-Rose C, et al. Long-term intellectual outcome in children with posterior fossa tumors according to radiation doses and volumes. Int J Radiat Oncol Biol Phys. 1999;45:137-45.

[21] Hoppe-Hirsch E, Brunet L, Laroussinie F, Cinalli G, Pierre-Kahn A, Renier D, et al. Intellectual outcome in children with malignant tumors of the posterior fossa: influence of the field of irradiation and quality of surgery. Childs Nerv Syst. 1995;11:340-5.

[22] Copeland DR, deMoor C, Moore BD, III, Ater JL. Neurocognitive development of children after a cerebellar tumor in infancy: A longitudinal study. J Clin Oncol. 1999;17:3476-86.

[23] Johnson DL, McCabe MA, Nicholson HS, Joseph AL, Getson PR, Byrne J, et al. Quality of long-term survival in young children with medulloblastoma. J Neurosurg. 1994;80:1004-10.

[24] Palmer SL, Goloubeva O, Reddick WE, Glass JO, Gajjar A, Kun L, et al. Patterns of intellectual development among survivors of pediatric medulloblastoma: a longitudinal analysis. J Clin Oncol. 2001;19:2302-8.

[25] Spiegler BJ, Bouffet E, Greenberg ML, Rutka JT, Mabbott DJ. Change in neurocognitive functioning after treatment with cranial radiation in childhood. J Clin Oncol. 2004;22:706-13.

[26] Radcliffe J, Bennett D, Kazak AE, Foley B, Phillips PC. Adjustment in childhood brain tumor survival: child, mother, and teacher report. J Pediatr Psychol. 1996;21:529-39.

[27] Seaver E, Geyer R, Sulzbacher S, Warner M, Batzel L, Milstein J, et al. Psychosocial adjustment in long-term survivors of childhood medulloblastoma and ependymoma treated with craniospinal irradiation. Pediatr Neurosurg. 1994;20:248-53.

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

[29] Packer RJ, Sutton LN, Atkins TE, Radcliffe J, Bunin GR, D'Angio G, et al. A prospective study of cognitive function in children receiving whole-brain radiotherapy and chemotherapy: 2-year results. J Neurosurg. 1989;70:707-13.

[30] Conklin HM, Li C, Xiong X, Ogg RJ, Merchant TE. Predicting change in academic abilities after conformal radiation therapy for localized ependymoma. J Clin Oncol. 2008;26:3965-70.

[31] Reeves CB, Palmer SL, Reddick WE, Merchant TE, Buchanan GM, Gajjar A, et al. Attention and memory functioning among pediatric patients with medulloblastoma. J Pediatr Psychol. 2006;31:272-80.

[32] Dennis M, Spiegler BJ, Obonsawin MC, Maria BL, Cowell C, Hoffman HJ, et al. Brain tumors in children and adolescents--III. Effects of radiation and hormone status on intelligence and on working, associative and serial-order memory. Neuropsychologia. 1992;30:257-75.

[33] Waber DP, Pomeroy SL, Chiverton AM, Kieran MW, Scott RM, Goumnerova LC, et al. Everyday cognitive function after craniopharyngioma in childhood. Pediatr Neurol. 2006;34:13-9.

[34] Fry AS, Hale S. Processing speed, working memory, and fluid intelligence: Evidence for a developmental cascade. Psychological Science. 1996;4:237-41.

[35] Filley CM, Kleinschmidt-DeMasters BK. Toxic leukoencephalopathy. N Engl J Med. 2001;345:425-32.

[36] Reddick WE, Russell JM, Glass JO, Xiong X, Mulhern RK, Langston JW, et al. Subtle white matter volume differences in children treated for medulloblastoma with conventional or reduced dose craniospinal irradiation. Magn Reson Imaging. 2000;18:787-93.

[37] Reddick WE, White HA, Glass JO, Wheeler GC, Thompson SJ, Gajjar A, et al. Developmental model relating white matter volume to neurocognitive deficits in pediatric brain tumor survivors. Cancer. 2003;97:2512-9.

[38] Jannoun L, Bloom HJ. Long-term psychological effects in children treated for intracranial tumors. Int J Radiat Oncol Biol Phys. 1990;18:747-53.

[39] Ellenberg L, McComb JG, Siegel SE, Stowe S. Factors affecting intellectual outcome in pediatric brain tumor patients. Neurosurgery. 1987;21:638-44.

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

[41] Merchant TE, Kiehna EN, Kun LE, Mulhern RK, Li C, Xiong X, et al. Phase II trial of conformal radiation therapy for pediatric patients with craniopharyngioma and correlation of surgical factors and radiation dosimetry with change in cognitive function. J Neurosurg. 2006;104:94-102.

[42] Di PM, Conklin HM, Li C, Xiong X, Merchant TE. Investigating verbal and visual auditory learning after conformal radiation therapy for childhood ependymoma. Int J Radiat Oncol Biol Phys. 2010;77:1002-8.

[43] Armstrong TS, Vera-Bolanos E, Gilbert MR. Clinical course of adult patients with ependymoma: Results of the Adult Ependymoma Outcomes Project. Cancer. 2011.

[44] Wetmore C, Herington D, Lin T, Onar-Thomas A, Gajjar A, Merchant TE. Reirradiation of recurrent medulloblastoma: does clinical benefit outweigh risk for toxicity? Cancer. 2014;120:3731-7.

[45] Adam K, Oswald I. Protein synthesis, bodily renewal and the sleep-wake cycle. Clin Sci (Lond). 1983;65:561-7.

[46] Spenceley SM. Sleep inquiry: a look with fresh eyes. Image J Nurs Sch. 1993;25:249-56.

[47] Amschler DH, McKenzie JF. Elementary students' sleep habits and teacher observations of sleep-related problems. J Sch Health. 2005;75:50-6.

[48] Lee KA, Stotts NA. Support of the growth hormone-somatomedin system to facilitate healing. Heart Lung. 1990;19:157-62.

[49] De KJ, Lorrain D, Gagnon P. Sleep positions and position shifts in five age groups: an ontogenetic picture. Sleep. 1992;15:143-9.

[50] Hayes MJ, Mitchell D. Spontaneous movements during sleep in children: temporal organization and changes with age. Dev Psychobiol. 1998;32:13-21.

[51] Lorrain D, De KJ. Sleep position and sleep stages: evidence of their independence. Sleep. 1998;21:335-40.

[52] Jones BE. Basic mechanisms of sleep-wake states. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. 4th ed. Philadelphia: Elsevier/Sanders; 2005. p. 136-53.

[53] Spilsbury JC, Storfer-Isser A, Drotar D, Rosen CL, Kirchner LH, Benham H, et al. Sleep behavior in an urban US sample of school-aged children. Arch Pediatr Adolesc Med. 2004;158:988-94.

[54] Beebe DW, Lewin D, Zeller M, McCabe M, MacLeod K, Daniels SR, et al. Sleep in overweight adolescents: shorter sleep, poorer sleep quality, sleepiness, and sleep-disordered breathing. J Pediatr Psychol. 2007;32:69-79.

[55] Chaput JP, Brunet M, Tremblay A. Relationship between short sleeping hours and childhood overweight/obesity: results from the 'Quebec en Forme' Project. Int J Obes (Lond). 2006;30:1080-5.

[56] Gregory AM, Rijsdijk FV, Eley TC. A twin-study of sleep difficulties in school-aged children. Child Dev. 2006;77:1668-79.

[57] Steriade M, Llinas RR. The functional states of the thalamus and the associated neuronal interplay. Physiol Rev. 1988;68:649-742.

[58] Steriade M, Llinas RR. Basic mechanisms of sleep generation. Neurology. 1992:9-17.

[59] Culebras A. The biology of sleep. Clinical handbook of sleep disorders. Boston: Butterworth-Heinemann; 1996. p. 13-51.

[60] Chou TC, Bjorkum AA, Gaus SE, Lu J, Scammell TE, Saper CB. Afferents to the ventrolateral preoptic nucleus. J Neurosci. 2002;22:977-90.

[61] Muller HL, Muller-Stover S, Gebhardt U, Kolb R, Sorensen N, Handwerker G. Secondary narcolepsy may be a causative factor of increased daytime sleepiness in obese childhood craniopharyngioma patients. J Pediatr Endocrinol Metab. 2006;19 Suppl 1:423-9.

[62] Llinas RR, Steriade M. Bursting of thalamic neurons and states of vigilance. J Neurophysiol. 2006;95:3297-308.

[63] Amzica F, Steriade M. Electrophysiological correlates of sleep delta waves. Electroencephalogr Clin Neurophysiol. 1998;107:69-83.

[64] Contreras D, Destexhe A, Sejnowski TJ, Steriade M. Spatiotemporal patterns of spindle oscillations in cortex and thalamus. J Neurosci. 1997;17:1179-96.

[65] Siegel JM. REM sleep. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep. Philadelphia: Elsevier Saunders; 2005. p. 120-35.

[66] Chase MH, Morales FR. Control of motoneurons during sleep. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. 4th ed. Philadelphia: Elsevier Saunders; 2005. p. 154-68.

[67] Mikkelsson L, Kaprio J, Kautiainen H, Kujala U, Mikkelsson M, Nupponen H. School fitness tests as predictors of adult health-related fitness. Am J Hum Biol. 2006;18:342-9.

[68] Gajdosik RL, Vander Linden DW, Williams AK. Concentric isokinetic torque characteristics of the calf muscles of active women aged 20 to 84 years. J Orthop Sports Phys Ther. 1999;29:181-90.

[69] Anders T, Sadeh A, Appareddy V. Normal sleep in neonates and children. Philadelphia: W.B. Saunders Company, 7-18; 1995.

[70] Mindell JA, Owens JA. A clinical guide to pediatric sleep: Diagnosis and management of sleep problems. Philadelphia, PA: Lippincott, Williams & Wilkins; 2003.

[71] National Sleep Foundation. 2007.

[72] Steriade M, Timofeev I, Grenier F. Natural waking and sleep states: a view from inside neocortical neurons. J Neurophysiol. 2001;85:1969-85.

[73] Faithfull S. Patients' experiences following cranial radiotherapy: a study of the somnolence syndrome. J Adv Nurs. 1991;16:939-46.

[74] Faithfull S, Brada M. Somnolence syndrome in adults following cranial irradiation for primary brain tumours. Clin Oncol (R Coll Radiol). 1998;10:250-4.

[75] D'Cruz OF, Vaughn BV, Gold SH, Greenwood RS. Symptomatic cataplexy in pontomedullary lesions. Neurology. 1994;44:2189-91.

[76] Greenough G, Sateia M, Fadul CE. Obstructive sleep apnea syndrome in a patient with medulloblastoma. Neuro Oncol. 1999;1:289-91.

[77] Ito K, Murofushi T, Mizuno M, Semba T. Pediatric brain stem gliomas with the predominant symptom of sleep apnea. Int J Pediatr Otorhinolaryngol. 1996;37:53-64.

[78] Sheridan F, Scharf D, Henderson VW, Miller CA. Lipomas of the mesencephalic tectum and rostral pons associated with sleep apnea syndrome. Clin Neuropathol. 1990;9:152-6.

[79] Pollak L, Shpirer I, Rabey JM, Klein C, Schiffer J. Polysomnography in patients with intracranial tumors before and after operation. Acta Neurol Scand. 2004;109:56-60.

[80] Rosen GM, Bendel AE, Neglia JP, Moertel CL, Mahowald M. Sleep in children with neoplasms of the central nervous system: case review of 14 children. Pediatrics. 2003;112:e46-e54.

[81] Sadeh A, Lavie P, Scher A, Tirosh E, Epstein R. Actigraphic home-monitoring sleep-disturbed and control infants and young children: a new method for pediatric assessment of sleep-wake patterns. Pediatrics. 1991;87:494-9.

[82] Sadeh A. Assessment of intervention for infant night waking: parental reports and activity-based home monitoring. J Consult Clin Psychol. 1994;62:63-8.

[83] Sadeh A. Evaluating night wakings in sleep-disturbed infants: a methodological study of parental reports and actigraphy. Sleep. 1996;19:757-62.

[84] Sadeh A, Acebo C, Seifer R, Aytur S, Carskadon MA. Activity-based assessment of sleep-wake patterns during the 1st year of life. Infant Behav Devel. 1995;18:329-37.

[85] Sadeh A, Hauri PJ, Kripke DF, Lavie P. The role of actigraphy in the evaluation of sleep disorders. Sleep. 1995;18:288-302.

[86] Sadeh A, Sharkey KM, Carskadon MA. Activity-based sleep-wake identification: an empirical test of methodological issues. Sleep. 1994;17:201-7.

[87] Dagan Y, Zeevi-Luria S, Sever Y, Hallis D, Yovel I, Sadeh A, et al. Sleep quality in children with attention deficit hyperactivity disorder: an actigraphic study. Psychiatry Clin Neurosci. 1997;51:383-6.

[88] Miller LG, Kraft IA. Application of actigraphy in the clinical setting: use in children with attention-deficit hyperactivity disorder. Pharmacotherapy. 1994;14:219-23.

[89] Cech DJ, Martin ST. Functional Movement Development Across the Life Span. 2nd ed. Philadelphia: W.B Sanders Company; 2002.

[90] Roebroeck ME, Jahnsen R, Carona C, Kent RM, Chamberlain MA. Adult outcomes and lifespan issues for people with childhood-onset physical disability. Dev Med Child Neurol. 2009;51:670-8.

[91] Edwards SL, Sarwark JF. Infant and child motor development. Clin Orthop Relat Res. 2005:33-9.

[92] Largo RH, Fischer JE, Rousson V. Neuromotor development from kindergarten age to adolescence: developmental course and variability. Swiss Med Wkly. 2003;133:193-9.

[93] McKay CM, Bell-Ellison BA, Wallace K, Ferron JM. A multilevel study of the associations between economic and social context, stage of adolescence, and physical activity and body mass index. Pediatrics. 2007;119 Suppl 1:S84-S91.

[94] Sisson SB, Broyles ST, Baker BL, Katzmarzyk PT. Screen time, physical activity, and overweight in U.S. youth: national survey of children's health 2003. J Adolesc Health. 2010;47:309-11.

[95] Paalanne NP, Korpelainen RI, Taimela SP, Auvinen JP, Tammelin TH, Hietikko TM, et al. Muscular fitness in relation to physical activity and television viewing among young adults. Med Sci Sports Exerc. 2009;41:1997-2002.

[96] McCrady SK, Levine JA. Sedentariness at work: how much do we really sit? Obesity (Silver Spring). 2009;17:2103-5.

[97] Jansson A, Saartok T, Werner S, Renstrom P. General joint laxity in 1845 Swedish school children of different ages: age- and gender-specific distributions. Acta Paediatr. 2004;93:1202-6.

[98] Woollacott MH, Burtner P. Neural and musculoskeletal contributions to the development of stance balance control in typical children and in children with cerebral palsy. Acta Paediatr Suppl. 1996;416:58-62.

[99] Malina RM, Bouchard C. Growth, Maturation and Physical Activity. Champaign, IL: Human Kinetics Press; 1991.

[100] Kisner CCL. Therapeutic Exercise: Foundations and Techniques. 5th ed. Philadelphia: F.A. Davis Company; 2002.

[101] Taeymans J, Clarys P, Abidi H, Hebbelinck M, Duquet W. Developmental changes and predictability of static strength in individuals of different maturity: a 30-year longitudinal study. J Sports Sci. 2009;27:833-41.

[102] American College of Sports Medicine: ACSM's Guidelines for Exercise Testing and Prescription. ed 7th. Baltimore, MD: Lippincott Williams & Wilkins; 2006.

[103] Armstrong N, Williams J, Balding J, Gentle P, Kirby B. The peak oxygen uptake of British children with reference to age, sex and sexual maturity. Eur J Appl Physiol Occup Physiol. 1991;62:369-75.

[104] Meyer K, Hajric R, Samek L, Baier M, Lauber P, Betz P, et al. Cardiopulmonary exercise capacity in healthy normals of different age. Cardiology. 1994;85:341-51.

[105] Rowland TW, Cunningham LN. Oxygen uptake plateau during maximal treadmill exercise in children. Chest. 1992;101:485-9.

[106] Rutenfranz J, AK L, V S, al e. Maximal aerobic power affected by maturation and body growth during childhood and adolescence. Eur J Pediatr 139:106-12. 1982.

[107] Ten Harkel AD, Takken T, Van Osch-Gevers M, Helbing WA. Normal values for cardiopulmonary exercise testing in children. Eur J Cardiovasc Prev Rehabil. 2010.

[108] Liu AK, Foreman NK, Gaspar LE, Trinidad E, Handler MH. Maximally safe resection followed by hypofractionated re-irradiation for locally recurrent ependymoma in children. Pediatr Blood Cancer. 2009;52:804-7.

[109] Armstrong GT, Liu Q, Yasui Y, Huang S, Ness KK, Leisenring W, et al. Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study. J Natl Cancer Inst. 2009;101:946-58.

[110] Ness KK, Mertens AC, Hudson MM, Wall MM, Leisenring WM, Oeffinger KC, et al. Limitations on physical performance and daily activities among long-term survivors of childhood cancer. Ann Intern Med. 2005;143:639-47.

[111] Ness KK, Morris EB, Nolan VG, Howell CR, Gilchrist LS, Stovall M, et al. Physical performance limitations among adult survivors of childhood brain tumors. Cancer. 2010;116:3034-44.

[112] Ness KK, Gurney JG, Zeltzer LK, Leisenring W, Mulrooney DA, Nathan PC, et al. The impact of limitations in physical, executive, and emotional function on health-related quality of

life among adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Arch Phys Med Rehabil. 2008;89:128-36.

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

[114] Combs SE, Kelter V, Welzel T, Behnisch W, Kulozik AE, Bischof M, et al. Influence of radiotherapy treatment concept on the outcome of patients with localized ependymomas. Int J Radiat Oncol Biol Phys. 2008;71:972-8.

[115] Stafford SL, Pollock BE, Foote RL, Gorman DA, Nelson DF, Schomberg PJ. Stereotactic radiosurgery for recurrent ependymoma. Cancer. 2000;88:870-5.

[116] Benesch M, Spiegl K, Winter A, Passini A, Lackner H, Moser A, et al. A scoring system to quantify late effects in children after treatment for medulloblastoma/ependymoma and its correlation with quality of life and neurocognitive functioning. Childs Nerv Syst. 2009;25:173-81.

[117] Rumpel H, Ho GL, Chan LL, Lim WE, Chong VF. Concomitant diminishing magnetization-transfer effect and increasing choline level in radiation-induced temporal-lobe changes. Australas Radiol. 2002;46:340-4.

[118] Haris M, Kumar S, Raj MK, Das KJ, Sapru S, Behari S, et al. Serial diffusion tensor imaging to characterize radiation-induced changes in normal-appearing white matter following radiotherapy in patients with adult low-grade gliomas. Radiat Med. 2008;26:140-50.

[119] Wang S, Wu EX, Qiu D, Leung LH, Lau HF, Khong PL. Longitudinal diffusion tensor magnetic resonance imaging study of radiation-induced white matter damage in a rat model. Cancer Res. 2009;69:1190-8.

[120] Bieri O, Scheffler K. Optimized balanced steady-state free precession magnetization transfer imaging. Magn Reson Med. 2007;58:511-8.

[121] Filippi M, Rocca MA. Magnetization transfer magnetic resonance imaging of the brain, spinal cord, and optic nerve. Neurotherapeutics. 2007;4:401-13.

[122] Mougin OE, Coxon RC, Pitiot A, Gowland PA. Magnetization transfer phenomenon in the human brain at 7 T. Neuroimage. 2010;49:272-81.

[123] Oberg B, Bergman T, Tropp H. Testing of isokinetic muscle strength in the ankle. Med Sci Sports Exerc. 1987;19:318-22.

[124] Fisniku LK, Altmann DR, Cercignani M, Tozer DJ, Chard DT, Jackson JS, et al. Magnetization transfer ratio abnormalities reflect clinically relevant grey matter damage in multiple sclerosis. Mult Scler. 2009;15:668-77.

[125] Ropele S, Fazekas F. Magnetization transfer MR imaging in multiple sclerosis. Neuroimaging Clin N Am. 2009;19:27-36.

[126] Garcia M, Gloor M, Bieri O, Wetzel SG, Radue EW, Scheffler K. MTR variations in normal adult brain structures using balanced steady-state free precession. Neuroradiology. 2011;53:159-67.

[127] Underhill HR, Yuan C, Yarnykh VL. Direct quantitative comparison between cross-relaxation imaging and diffusion tensor imaging of the human brain at 3.0 T. Neuroimage. 2009;47:1568-78.

[128] Woolrich MW, Jbabdi S, Patenaude B, Chappell M, Makni S, Behrens T, et al. Bayesian analysis of neuroimaging data in FSL. Neuroimage. 2009;45:S173-S86.

[129] Khong PL, Kwong DL, Chan GC, Sham JS, Chan FL, Ooi GC. Diffusion-tensor imaging for the detection and quantification of treatment-induced white matter injury in children with medulloblastoma: a pilot study. AJNR Am J Neuroradiol. 2003;24:734-40.

[130] Nagesh V, Tsien CI, Chenevert TL, Ross BD, Lawrence TS, Junick L, et al. Radiation-induced changes in normal-appearing white matter in patients with cerebral tumors: a diffusion tensor imaging study. Int J Radiat Oncol Biol Phys. 2008;70:1002-10.

[131] Qiu D, Leung LH, Kwong DL, Chan GC, Khong PL. Mapping radiation dose distribution on the fractional anisotropy map: applications in the assessment of treatment-induced white matter injury. Neuroimage. 2006;31:109-15.

[132] Rueckriegel SM, Driever PH, Blankenburg F, Ludemann L, Henze G, Bruhn H. Differences in supratentorial damage of white matter in pediatric survivors of posterior fossa tumors with and without adjuvant treatment as detected by magnetic resonance diffusion tensor imaging. Int J Radiat Oncol Biol Phys. 2010;76:859-66.

[133] Hoon AH, Jr., Stashinko EE, Nagae LM, Lin DD, Keller J, Bastian A, et al. Sensory and motor deficits in children with cerebral palsy born preterm correlate with diffusion tensor imaging abnormalities in thalamocortical pathways. Dev Med Child Neurol. 2009;51:697-704.

[134] Kim CH, Chung CK, Kim JS, Jahng TA, Lee JH, Song IC. Use of diffusion tensor imaging to evaluate weakness. J Neurosurg. 2007;106:111-8.

[135] Lui YW, Law M, Chacko-Mathew J, Babb JS, Tuvia K, Allen JC, et al. Brainstem corticospinal tract diffusion tensor imaging in patients with primary posterior fossa neoplasms stratified by tumor type:a study of association with motor weakness and outcome. Neurosurgery. 2007;61:1199-207.

[136] Yokoyama K, Matsuki M, Shimano H, Sumioka S, Ikenaga T, Hanabusa K, et al. Diffusion tensor imaging in chronic subdural hematoma: correlation between clinical signs and fractional anisotropy in the pyramidal tract. AJNR Am J Neuroradiol. 2008;29:1159-63.

[137] Mayo C, Yorke E, Merchant TE. Radiation associated brainstem injury. Int J Radiat Oncol Biol Phys. 2010;76:S36-S41.

[138] Price SJ, Gillard JH. Imaging biomarkers of brain tumour margin and tumour invasion. Br J Radiol. 2011;84 Spec No 2:S159-S67.

[139] Sternberg EJ, Lipton ML, Burns J. Utility of diffusion tensor imaging in evaluation of the peritumoral region in patients with primary and metastatic brain tumors. AJNR Am J Neuroradiol. 2014;35:439-44.

[140] Sundgren PC, Fan X, Weybright P, Welsh RC, Carlos RC, Petrou M, et al. Differentiation of recurrent brain tumor versus radiation injury using diffusion tensor imaging in patients with new contrast-enhancing lesions. Magn Reson Imaging. 2006;24:1131-42.

[141] Paulson ES, Schmainda KM. Comparison of dynamic susceptibility-weighted contrast-enhanced MR methods: recommendations for measuring relative cerebral blood volume in brain tumors. Radiology. 2008;249:601-13.

[142] Akella NS, Twieg DB, Mikkelsen T, Hochberg FH, Grossman S, Cloud GA, et al. Assessment of brain tumor angiogenesis inhibitors using perfusion magnetic resonance imaging: quality and analysis results of a phase I trial. J Magn Reson Imaging. 2004;20:913-22.

[143] Fuss M, Wenz F, Essig M, Muenter M, Debus J, Herman TS, et al. Tumor angiogenesis of low-grade astrocytomas measured by dynamic susceptibility contrast-enhanced MRI (DSC-MRI) is predictive of local tumor control after radiation therapy. Int J Radiat Oncol Biol Phys. 2001;51:478-82.

[144] Law M, Oh S, Johnson G, Babb JS, Zagzag D, Golfinos J, et al. Perfusion magnetic resonance imaging predicts patient outcome as an adjunct to histopathology: a second reference standard in the surgical and nonsurgical treatment of low-grade gliomas. Neurosurgery. 2006;58:1099-107.

[145] Maia AC, Jr., Malheiros SM, da Rocha AJ, da Silva CJ, Gabbai AA, Ferraz FA, et al. MR cerebral blood volume maps correlated with vascular endothelial growth factor expression and tumor grade in nonenhancing gliomas. AJNR Am J Neuroradiol. 2005;26:777-83.

[146] Ulmer S, Liess C, Kesari S, Otto N, Straube T, Jansen O. Use of dynamic susceptibility-contrast MRI (DSC-MRI) to assess perfusion changes in the ipsilateral brain parenchyma from glioblastoma. J Neurooncol. 2009;91:213-20.

[147] Krasin MJ, Spalding AC, Navid F, Hoth K, Hua CH, Merchant TE, et al. Tumor and systemic cytokine response in patients with pediatric sarcoma treated with limited margin 3DCRT and IMRT. Int J Radiat Oncol Biol Phys. 2010.

[148] Merchant TE, Hua CH, Shukla H, Ying X, Nill S, Oelfke U. Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive function. Pediatr Blood Cancer. 2008;51:110-7.

[149] Spalding AC, Wu S, Xiong X, Elliot J, Merchant TE. Suppression of Eosinophilic Inflammatory Response during Radiation Predicts Clinical Outcome in Pediatric Brain Tumors. Int J Radiat Oncol Biol Phys. 2009;75:S39-S40.

[150] Fletcher MA, Zeng XR, Barnes Z, Levis S, Klimas NG. Plasma cytokines in women with chronic fatigue syndrome. J Transl Med. 2009;7:96.

[151] Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med. 2005;352:1685-95.

[152] Jakobsson S, Ahlberg K, Taft C, Ekman T. Exploring a link between fatigue and intestinal injury during pelvic radiotherapy. Oncologist. 2010;15:1009-15.

[153] Polistena A, Johnson LB, Ohiami-Masseron S, Wittgren L, Back S, Thornberg C, et al. Local radiotherapy of exposed murine small bowel: apoptosis and inflammation. BMC Surg. 2008;8:1.

[154] Brouwers P. Commentary: study of the neurobehavioral consequences of childhood cancer: entering the genomic era? J Pediatr Psychol. 2005;30:79-84.

[155] Butler RW, Mulhern RK. Neurocognitive interventions for children and adolescents surviving cancer. J Pediatr Psychol. 2005;30:65-78.

[156] Moore BD, III. Neurocognitive outcomes in survivors of childhood cancer. J Pediatr Psychol. 2005;30:51-63.

[157] Mabbott DJ, Snyder JJ, Penkman L, Witol A. The effects of treatment for posterior fossa brain tumors on selective attention. J Int Neuropsychol Soc. 2009;15:205-16.

[158] Riva D, Pantaleoni C, Milani N, Fossati BF. Impairment of neuropsychological functions in children with medulloblastomas and astrocytomas in the posterior fossa. Childs Nerv Syst. 1989;5:107-10.

[159] Lafay-Cousin L, Bouffet E, Hawkins C, Amid A, Huang A, Mabbott DJ. Impact of radiation avoidance on survival and neurocognitive outcome in infant medulloblastoma. Curr Oncol. 2009;16:21-8.

[160] Khedhaier A, Remadi S, Corbex M, Ahmed SB, Bouaouina N, Mestiri S, et al. Glutathione S-transferases (GSTT1 and GSTM1) gene deletions in Tunisians: susceptibility and prognostic implications in breast carcinoma. Br J Cancer. 2003;89:1502-7.

[161] Barahmani N, Carpentieri S, Li XN, Wang T, Cao Y, Howe L, et al. Glutathione S-transferase M1 and T1 polymorphisms may predict adverse effects after therapy in children with medulloblastoma. Neuro Oncol. 2009;11:292-300.

[162] Andreassen CN, Alsner J, Overgaard M, Overgaard J. Prediction of normal tissue radiosensitivity from polymorphisms in candidate genes. Radiother Oncol. 2003;69:127-35.

[163] Fernet M, Hall J. Genetic biomarkers of therapeutic radiation sensitivity. DNA Repair (Amst). 2004;3:1237-43.

[164] Gutierrez-Enriquez S, Fernet M, Dork T, Bremer M, Lauge A, Stoppa-Lyonnet D, et al. Functional consequences of ATM sequence variants for chromosomal radiosensitivity. Genes Chromosomes Cancer. 2004;40:109-19.

[165] Ho AY, Atencio DP, Peters S, Stock RG, Formenti SC, Cesaretti JA, et al. Genetic predictors of adverse radiotherapy effects: the Gene-PARE project. Int J Radiat Oncol Biol Phys. 2006;65:646-55.

[166] Anney R, Klei L, Pinto D, Regan R, Conroy J, Magalhaes TR, et al. A genome-wide scan for common alleles affecting risk for autism. Hum Mol Genet. 2010;19:4072-82.

[167] Kim HL, Satta Y. Population genetic analysis of the N-acylsphingosine amidohydrolase gene associated with mental activity in humans. Genetics. 2008;178:1505-15.

[168] Noor A, Whibley A, Marshall CR, Gianakopoulos PJ, Piton A, Carson AR, et al. Disruption at the PTCHD1 Locus on Xp22.11 in Autism spectrum disorder and intellectual disability. Sci Transl Med. 2010;2:49ra68.

[169] Pagnamenta AT, Khan H, Walker S, Gerrelli D, Wing K, Bonaglia MC, et al. Rare familial 16q21 microdeletions under a linkage peak implicate cadherin 8 (CDH8) in susceptibility to autism and learning disability. J Med Genet. 2011;48:48-54.

[170] Skuse DH. X-linked genes and mental functioning. Hum Mol Genet. 2005;14 Spec No 1:R27-R32.

[171] Hawkins CE, Walker E, Mohamed N, Zhang C, Jacob K, Shirinian M, et al. BRAF-KIAA1549 fusion predicts better clinical outcome in pediatric low grade astrocytoma. Clin Cancer Res. 2011.

[172] Tabori U, Wong V, Ma J, Shago M, Alon N, Rutka J, et al. Telomere maintenance and dysfunction predict recurrence in paediatric ependymoma. Br J Cancer. 2008;99:1129-35.

[173] Debaun MR, Derdeyn CP, McKinstry RC, III. Etiology of strokes in children with sickle cell anemia. Ment Retard Dev Disabil Res Rev. 2006;12:192-9.

[174] Hoppe C, Klitz W, Cheng S, Apple R, Steiner L, Robles L, et al. Gene interactions and stroke risk in children with sickle cell anemia. Blood. 2004;103:2391-6.

[175] Kirkham FJ. Is there a genetic basis for pediatric stroke? Curr Opin Pediatr. 2003;15:547-58.

[176] Ganesan V, Prengler M, Wade A, Kirkham FJ. Clinical and radiological recurrence after childhood arterial ischemic stroke. Circulation. 2006;114:2170-7.

[177] Voetsch B, Jin RC, Bierl C, Benke KS, Kenet G, Simioni P, et al. Promoter polymorphisms in the plasma glutathione peroxidase (GPx-3) gene: a novel risk factor for arterial ischemic stroke among young adults and children. Stroke. 2007;38:41-9.

[178] Onda H, Kasuya H, Yoneyama T, Takakura K, Hori T, Takeda J, et al. Genomewide-linkage and haplotype-association studies map intracranial aneurysm to chromosome 7q11. Am J Hum Genet. 2001;69:804-19.

[179] Yoneyama T, Kasuya H, Onda H, Akagawa H, Hashiguchi K, Nakajima T, et al. Collagen type I alpha2 (COL1A2) is the susceptible gene for intracranial aneurysms. Stroke. 2004;35:443-8.

[180] Inoue K, Mineharu Y, Inoue S, Yamada S, Matsuda F, Nozaki K, et al. Search on chromosome 17 centromere reveals TNFRSF13B as a susceptibility gene for intracranial aneurysm: a preliminary study. Circulation. 2006;113:2002-10.

[181] Onouchi Y, Gunji T, Burns JC, Shimizu C, Newburger JW, Yashiro M, et al. ITPKC functional polymorphism associated with Kawasaki disease susceptibility and formation of coronary artery aneurysms. Nat Genet. 2008;40:35-42.

[182] Seidman C, Kirkham F, Pavlakis S. Pediatric stroke: current developments. Curr Opin Pediatr. 2007;19:657-62.

[183] Kitahara T, Okumura K, Semba A, Yamaura A, Makino H. Genetic and immunologic analysis on moya-moya. J Neurol Neurosurg Psychiatry. 1982;45:1048-52.

[184] Finsterer J, Fellinger J. Nuclear and mitochondrial genes mutated in nonsyndromic impaired hearing. Int J Pediatr Otorhinolaryngol. 2005;69:621-47.

[185] Gurtler N, Lalwani AK. Etiology of syndromic and nonsyndromic sensorineural hearing loss. Otolaryngol Clin North Am. 2002;35:891-908.

[186] Smith RJ, Hone S. Genetic screening for deafness. Pediatr Clin North Am. 2003;50:315-29.

[187] Oguchi T, Ohtsuka A, Hashimoto S, Oshima A, Abe S, Kobayashi Y, et al. Clinical features of patients with GJB2 (connexin 26) mutations: severity of hearing loss is correlated with genotypes and protein expression patterns. J Hum Genet. 2005;50:76-83.

[188] Brummett RE, Morrison RB. The incidence of aminoglycoside antibiotic-induced hearing loss. Arch Otolaryngol Head Neck Surg. 1990;116:406-10.

[189] Usami S, Abe S, Shinkawa H, Kimberling WJ. Sensorineural hearing loss caused by mitochondrial DNA mutations: special reference to the A1555G mutation. J Commun Disord. 1998;31:423-34.

[190] Prezant TR, Agapian JV, Bohlman MC, Bu X, Oztas S, Qiu WQ, et al. Mitochondrial ribosomal RNA mutation associated with both antibiotic-induced and non-syndromic deafness. Nat Genet. 1993;4:289-94.

[191] He XY, Wang YY, Dai P, Gu J, Chen TJ. Development of a molecular screening test for hereditary hearing loss and genetic susceptibility to aminoglycoside toxicity for Chinese population. Beijing Da Xue Xue Bao. 2005;37:51-4.

[192] Weatherly RA, Owens JJ, Catlin FI, Mahoney DH. cis-platinum ototoxicity in children. Laryngoscope. 1991;101:917-24.

[193] Oldenburg J, Kraggerud SM, Cvancarova M, Lothe RA, Fossa SD. Cisplatin-induced long-term hearing impairment is associated with specific glutathione s-transferase genotypes in testicular cancer survivors. J Clin Oncol. 2007;25:708-14.

[194] Riedemann L, Lanvers C, Deuster D, Peters U, Boos J, Jurgens H, et al. Megalin genetic polymorphisms and individual sensitivity to the ototoxic effect of cisplatin. Pharmacogenomics J. 2008;8:23-8.

[195] Knoll C, Smith RJ, Shores C, Blatt J. Hearing genes and cisplatin deafness: a pilot study. Laryngoscope. 2006;116:72-4.

[196] Castellvi-Bel S, Mila M. Genes responsible for nonspecific mental retardation. Mol Genet Metab. 2001;72:104-8.

[197] Flint J. The genetic basis of cognition. Brain. 1999;122 (Pt 11):2015-32.

[198] Najmabadi H, Motazacker MM, Garshasbi M, Kahrizi K, Tzschach A, Chen W, et al. Homozygosity mapping in consanguineous families reveals extreme heterogeneity of non-syndromic autosomal recessive mental retardation and identifies 8 novel gene loci. Hum Genet. 2007;121:43-8.

[199] Gosso MF, de Geus EJ, Polderman TJ, Boomsma DI, Heutink P, Posthuma D. Common variants underlying cognitive ability: further evidence for association between the SNAP-25 gene and cognition using a family-based study in two independent Dutch cohorts. Genes Brain Behav. 2008;7:355-64.

[200] Gozal D, Capdevila OS, Kheirandish-Gozal L, Crabtree VM. APOE epsilon 4 allele, cognitive dysfunction, and obstructive sleep apnea in children. Neurology. 2007;69:243-9.

[201] Kheirandish L, Row BW, Li RC, Brittian KR, Gozal D. Apolipoprotein E-deficient mice exhibit increased vulnerability to intermittent hypoxia-induced spatial learning deficits. Sleep. 2005;28:1412-7.

[202] Krajinovic M, Robaey P, Chiasson S, Lemieux-Blanchard E, Rouillard M, Primeau M, et al. Polymorphisms of genes controlling homocysteine levels and IQ score following the treatment for childhood ALL. Pharmacogenomics. 2005;6:293-302.

[203] Law N, Bouffet E, Laughlin S, Laperriere N, Briere ME, Strother D, et al. Cerebello-thalamo-cerebral connections in pediatric brain tumor patients: Impact on working memory. Neuroimage. 2011;56:2238-48.

[204] Merchant TE, Li C, Xiong X, Gaber MW. Cytokine and growth factor responses after radiotherapy for localized ependymoma. Int J Radiat Oncol Biol Phys. 2009;74:159-67.

[205] Parker, al. e. 2013.

[206] Witt H, Mack SC, Ryzhova M, Bender S, Sill M, Isserlin R, et al. Delineation of two clinically and molecularly distinct subgroups of posterior fossa ependymoma. Cancer Cell. 2011;20:143-57.

[207] Punchihewa ea. 2013.

[208] Ramaswamy V, Remke M, Bouffet E, Faria CC, Perreault S, Cho YJ, et al. Recurrence patterns across medulloblastoma subgroups: an integrated clinical and molecular analysis. Lancet Oncol. 2013;14:1200-7.

[209] Nishio T, Sato T, Kitamura H, Murakami K, Ogino T. Distributions of beta+ decayed nuclei generated in the CH2 and H2O targets by the target nuclear fragment reaction using therapeutic MONO and SOBP proton beam. Med Phys. 2005;32:1070-82.

[210] Vynckier S, Derreumaux S, Richard F, Bol A, Michel C, Wambersie A. Is it possible to verify directly a proton-treatment plan using positron emission tomography? Radiother Oncol. 1993;26:275-7.

[211] Parodi K, Enghardt W, Haberer T. In-beam PET measurements of beta+ radioactivity induced by proton beams. Phys Med Biol. 2002;47:21-36.

[212] Pshenichnov I, Larionov A, Mishustin I, Greiner W. PET monitoring of cancer therapy with 3He and 12C beams: a study with the GEANT4 toolkit. Phys Med Biol. 2007;52:7295-312.

[213] Tabori U. Observation or Radiation Therapy and/or Chemotherapy and Second Surgery in Treating Children Who Have Undergone Surgery for Ependymoma - ACNS0121. clinicaltrial gov NCT000278462013.

[214] Smith A. Maintenance Chemotherapy or Observation Following Induction Chemotherapy and Radiation Therapy in Treating Younger Patients with Newly Diagnosed Ependymoma. clinicaltrials gov - NCT0109636802013.

[215] Wright KD. Phase I Study of 5-Fluorouracil in Children and Young Adults with Recurrent Ependymoma - SJREFU. clinicaltrial gov - NCT0149878302013.

[216] ICRU. Prescribing, Recording, and Reporting Photon Beam Therapy. Report No. 50. In: (ICRU) ICoRUaM, editor. Bethesda, MD1993.

[217] ICRU. Prescribing, Recording, and Reporting Photon Beam Therapy. (Supplement to ICRU Report 50). Bethesda, MD1999.

[218] ICRU. Prescribing, Recording, and Reporting Proton-Beam Therapy. Oxford, UK2007.

[219] Quick Speech-in-Noise Test [Audio CD]. Elk Grove Village, IL.2001.

[220] Bamford-Kowal-Bench Speech-in-Noise Test [Audio CD]. Elk Grove Village, IL.2005.

[221] Wechsler D. Wechsler Intelligence Scale for Children. San Antonio, TX: Pearson; 2003.

[222] Wechsler D. Wechsler Adult Intelligence Scale. San Antonio, TX: Pearson; 2008.

[223] Wechsler D. Wechsler Preschool and Primary Scale of Intelligence. San Antonio, TX: Pearson; 2002.

[224] Mollica CM, Maruff P, Collie A, Vance A. Repeated assessment of cognition in children and the measurement of performance change. Child Neuropsychol. 2005;11:303-10.

[225] Falleti MG, Maruff P, Collie A, Darby DG. Practice effects associated with the repeated assessment of cognitive function using the CogState battery at 10-minute, one week and one month test-retest intervals. J Clin Exp Neuropsychol. 2006;28:1095-112.

[226] Betts J, McKay J, Maruff P, Anderson V. The development of sustained attention in children: the effect of age and task load. Child Neuropsychol. 2006;12:205-21.

[227] Snyder AM, Maruff P, Pietrzak RH, Cromer JR, Snyder PJ. Effect of treatment with stimulant medication on nonverbal executive function and visuomotor speed in children with attention deficit/hyperactivity disorder (ADHD). Child Neuropsychol. 2008;14:211-26.

[228] Collie A, Makdissi M, Maruff P, Bennell K, McCrory P. Cognition in the days following concussion: comparison of symptomatic versus asymptomatic athletes. J Neurol Neurosurg Psychiatry. 2006;77:241-5.

[229] Vardy J, Wong K, Yi QL, Park A, Maruff P, Wagner L, et al. Assessing cognitive function in cancer patients. Support Care Cancer. 2006;14:1111-8.

[230] Woodcook R, Mcgrew K, Mather N. Woodcock-Johnson III (WJ-III). Riverside Publishing; 2001.

[231] Gioia GA, Isquith, P.K., Guy, S.G., Kenworthy, L. The Behavior Rating Inventory of Executive Function (BRIEF). Lutz, FL: Psychological Assessment Resources, Incorporated; 2001.

[232] Beery KE, Buktenica NA, Beery NA. The Beery-Buktenica Developmental Test of Visual-Motor Integration: Administration, Scoring and Teaching. Sixth Edition; Beery VMI ed. San Antonio, TX: Pearson; 2010.

[233] Delis DC, Kramer JH, Kaplan E, Ober BA. California Verbal Learning Test - Children's Edition (CVLT-CT). Children ed. San Antonio, TX: Pearson; 2010.

[234] Delis DC, Kramer JH, Kaplan E, Ober BA. California Verbal Learning Test - Second Edition, Adult Version (CVLT-II). Second ed. San Antonio, TX: Pearson; 2000.

[235] Tiffin J. Purdue Pegborad: Examiner Manual. In: Associates SR, editor. Chicago, IL1968.

[236] Bracken BA. Bracken Basic Concept Scale. Third Edition: Receptive (BBCS-3:R) ed. San Antonio, TX: Pearson; 2006.

[237] Reynolds CR, Kamphaus RW. Behavior Assessment System for Children. Second Edition (BASC-II) ed. San Antonio, TX: Pearson; 2004.

[238] Derogatis LR. Brief Symptom Inventory (BSI). San Antonio, TX: Pearson; 1993.

[239] Palmer SN, Meeske KA, Katz ER, Burwinkle TM, Varni JW. The PedsQL Brain Tumor Module: initial reliability and validity. Pediatr Blood Cancer. 2007;49:287-93.

[240] Varni JW, Katz ER, Seid M, Quiggins DJ, Friedman-Bender A. The pediatric cancer quality of life inventory-32 (PCQL-32): I. Reliability and validity. Cancer. 1998;82:1184-96.

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

[242] Sainio P, Koskinen S, Heliovaara M, Martelin T, Harkanen T, Hurri H, et al. Self-reported and test-based mobility limitations in a representative sample of Finns aged 30+. Scand J Public Health. 2006;34:378-86.

[243] Bruininks RH, Bruininks BD. BOT2 Bruiniks-Oseretsky Test of Motor Proficiency. 2nd ed. Circle Pines, MN: AGS Publishing; 2005.

[244] Reuben DB, Siu AL. An objective measure of physical function of elderly outpatients. The Physical Performance Test. J Am Geriatr Soc. 1990;38:1105-12.

[245] Rozzini R, Frisoni GB, Bianchetti A, Zanetti O, Trabucchi M. Physical Performance Test and Activities of Daily Living scales in the assessment of health status in elderly people. J Am Geriatr Soc. 1993;41:1109-13.

[246] Rozzini R, Frisoni GB, Ferrucci L, Barbisoni P, Bertozzi B, Trabucchi M. The effect of chronic diseases on physical function. Comparison between activities of daily living scales and the Physical Performance Test. Age Ageing. 1997;26:281-7.

[247] Simmonds MJ. Physical function in patients with cancer: psychometric characteristics and clinical usefulness of a physical performance test battery. J Pain Symptom Manage. 2002;24:404-14.

[248] Klipstein-Grobusch K, Georg T, Boeing H. Interviewer variability in anthropometric measurements and estimates of body composition. Int J Epidemiol. 1997;26 Suppl 1:S174-S80.

[249] Taylor RW, Keil D, Gold EJ, Williams SM, Goulding A. Body mass index, waist girth, and waist-to-hip ratio as indexes of total and regional adiposity in women: evaluation using receiver operating characteristic curves. Am J Clin Nutr. 1998;67:44-9.

[250] Biodex. Isokinetic testing and data interpretation normative database. 2007.

[251] Boone DC, Azen SP, Lin CM, Spence C, Baron C, Lee L. Reliability of goniometric measurements. Phys Ther. 1978;58:1355-60.

[252] Brosseau L, Balmer S, Tousignant M, O'Sullivan JP, Goudreault C, Goudreault M, et al. Intra- and intertester reliability and criterion validity of the parallelogram and universal goniometers for measuring maximum active knee flexion and extension of patients with knee restrictions. Arch Phys Med Rehabil. 2001;82:396-402.

[253] Gajdosik RL, Bohannon RW. Clinical measurement of range of motion. Review of goniometry emphasizing reliability and validity. Phys Ther. 1987;67:1867-72.

[254] Baggett BD, Young G. Ankle joint dorsiflexion. Establishment of a normal range. J Am Podiatr Med Assoc. 1993;83:251-4.

[255] Moseley AM, Crosbie J, Adams R. Normative data for passive ankle plantarflexion--dorsiflexion flexibility. Clin Biomech (Bristol , Avon). 2001;16:514-21.

[256] Norkin CC, White DJ. Measurement of Joint Motion: A Guide to Goniometry. Philadelphis: F.A.D. Company; 1985.

[257] Butterfeld SA, Lehnhard RA, Coladarci T. Age, sex, and body mass index in performance of selected locomotor and fitness tasks by children in grades K-2. Percept Mot Skills. 2002;94:80-6.

[258] Patterson P, Wiksten DL, Ray L, Flanders C, Sanphy D. The validity and reliability of the back saver sit-and-reach test in middle school girls and boys. Res Q Exerc Sport. 1996;67:448-51.

[259] Levangie PK, Norkin CC. Joint Structure and Function: a Comprehensive Analysis. 3rd ed. Philadelphia: F.A.D. Company; 2001.

[260] Cohen H, Heaton LG, Congdon SL, Jenkins HA. Changes in sensory organization test scores with age. Age Ageing. 1996;25:39-44.

[261] Borah D, Wadhwa S, Singh U, Yadav SL, Bhattacharjee M, Sindhu V. Age related changes in postural stability. Indian J Physiol Pharmacol. 2007;51:395-404.

[262] Broglio SP, Ferrara MS, Sopiarz K, Kelly MS. Reliable change of the sensory organization test. Clin J Sport Med. 2008;18:148-54.

[263] Casselbrant ML, Mandel EM, Sparto PJ, Perera S, Redfern MS, Fall PA, et al. Longitudinal posturography and rotational testing in children three to nine years of age: normative data. Otolaryngol Head Neck Surg. 2010;142:708-14.

[264] Gagnon I, Swaine B, Forget R. Exploring the comparability of the Sensory Organization Test and the Pediatric Clinical Test of Sensory Interaction for Balance in children. Phys Occup Ther Pediatr. 2006;26:23-41.

[265] Mirka A, Black FO. Clinical application of dynamic posturography for evaluating sensory integration and vestibular dysfunction. Neurol Clin. 1990;8:351-9.

[266] Riley MA, Clark S. Recurrence analysis of human postural sway during the sensory organization test. Neurosci Lett. 2003;342:45-8.

[267] Steindl R, Kunz K, Schrott-Fischer A, Scholtz AW. Effect of age and sex on maturation of sensory systems and balance control. Dev Med Child Neurol. 2006;48:477-82.

[268] Valente M. Maturational effects of the vestibular system: a study of rotary chair, computerized dynamic posturography, and vestibular evoked myogenic potentials with children. J Am Acad Audiol. 2007;18:461-81.

[269] Wrisley DM, Stephens MJ, Mosley S, Wojnowski A, Duffy J, Burkard R. Learning effects of repetitive administrations of the sensory organization test in healthy young adults. Arch Phys Med Rehabil. 2007;88:1049-54.

[270] Oxford GK, Vogel KA, Le V, Mitchell A, Muniz S, Vollmer MA. Adult norms for a commercially available Nine Hole Peg Test for finger dexterity. Am J Occup Ther. 2003;57:570-3.

[271] Smith YA, Hong E, Presson C. Normative and validation studies of the Nine-hole Peg Test with children. Percept Mot Skills. 2000;90:823-43.

[272] du Montcel ST, Charles P, Ribai P, Goizet C, Le BA, Labauge P, et al. Composite cerebellar functional severity score: validation of a quantitative score of cerebellar impairment. Brain. 2008;131:1352-61.

[273] Habrand JL, Saran F, Alapetite C, Noel G, El Boustany R, Grill J. Radiation therapy in the management of craniopharyngioma: current concepts and future developments. J Pediatr Endocrinol Metab. 2006;19 Suppl 1:389-94.

[274] Schmahmann JD, Gardner R, MacMore J, Vangel MG. Development of a brief ataxia rating scale (BARS) based on a modified form of the ICARS. Mov Disord. 2009;24:1820-8.

[275] Akima H, Kano Y, Enomoto Y, Ishizu M, Okada M, Oishi Y, et al. Muscle function in 164 men and women aged 20-84 yr. Med Sci Sports Exerc. 2001;33:220-6.

[276] Baron R. Normative data for muscle strength in relation to age, knee angle and velocity. Wien Med Wochenschr. 1995;145:600-6.

[277] Holm I, Fredriksen P, Fosdahl M, Vollestad N. A normative sample of isotonic and isokinetic muscle strength measurements in children 7 to 12 years of age. Acta Paediatr. 2008;97:602-7.

[278] Holmback AM, Porter MM, Downham D, Lexell J. Reliability of isokinetic ankle dorsiflexor strength measurements in healthy young men and women. Scand J Rehabil Med. 1999;31:229-39.

[279] Knapik JJ, Wright JE, Mawdsley RH, Braun J. Isometric, isotonic, and isokinetic torque variations in four muscle groups through a range of joint motion. Phys Ther. 1983;63:938-47.

[280] Knapik JJ, Wright JE, Mawdsley RH, Braun JM. Isokinetic, isometric and isotonic strength relationships. Arch Phys Med Rehabil. 1983;64:77-80.

[281] Martin HJ, Yule V, Syddall HE, Dennison EM, Cooper C, Aihie SA. Is hand-held dynamometry useful for the measurement of quadriceps strength in older people? A comparison with the gold standard Bodex dynamometry. Gerontology. 2006;52:154-9.

[282] Merlini L, Dell'Accio D, Granata C. Reliability of dynamic strength knee muscle testing in children. J Orthop Sports Phys Ther. 1995;22:73-6.

[283] Neder JA, Nery LE, Shinzato GT, Andrade MS, Peres C, Silva AC. Reference values for concentric knee isokinetic strength and power in nonathletic men and women from 20 to 80 years old. J Orthop Sports Phys Ther. 1999;29:116-26.

[284] Perrin DH. Isokinetic exercise and assessment. Champaign, IL: Human Kinetics Publishers; 1993.

[285] Sunnerhagen KS, Hedberg M, Henning GB, Cider A, Svantesson U. Muscle performance in an urban population sample of 40- to 79-year-old men and women. Scand J Rehabil Med. 2000;32:159-67.

[286] Wiggin M, Wilkinson K, Habetz S, Chorley J, Watson M. Percentile values of isokinetic peak torque in children six through thirteen years old. Pediatr Phys Ther. 2006;18:3-18.

[287] Yoon TS, Park DS, Kang SW, Chun SI, Shin JS. Isometric and isokinetic torque curves at the knee joint. Yonsei Med J. 1991;32:33-43.

[288] Mathiowetz V, Kashman N, Volland G, Weber K, Dowe M, Rogers S. Grip and pinch strength: normative data for adults. Arch Phys Med Rehabil. 1985;66:69-74.

[289] Mathiowetz V, Weber K, Volland G, Kashman N. Reliability and validity of grip and pinch strength evaluations. J Hand Surg Am. 1984;9:222-6.

[290] Mathiowetz V, Wiemer DM, Federman SM. Grip and pinch strength: norms for 6- to 19-year-olds. Am J Occup Ther. 1986;40:705-11.

[291] Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26:319-38.

[292] MacIntyre N, Crapo RO, Viegi G, Johnson DC, van der Grinten CP, Brusasco V, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J. 2005;26:720-35.

[293] Ventham JC, Reilly JJ. Reproducibility of resting metabolic rate measurement in children. Br J Nutr. 1999;81:435-7.

[294] Paridon SM, Alpert BS, Boas SR, Cabrera ME, Caldarera LL, Daniels SR, et al. Clinical stress testing in the pediatric age group: a statement from the American Heart Association Council on Cardiovascular Disease in the Young, Committee on Atherosclerosis, Hypertension, and Obesity in Youth. Circulation. 2006;113:1905-20.

[295] Doxey D, Bruce D, Sklar F, Swift D, Shapiro K. Posterior fossa syndrome: identifiable risk factors and irreversible complications. Pediatr Neurosurg. 1999;31:131-6.

[296] Murphy ES, Merchant TE, Wu S, Xiong X, Lukose R, Wright KD, et al. Necrosis after craniospinal irradiation: Results from a prospective series of children with CNS embryonal tumors. Int J Radiat Oncol Biol Phys. 2012;In Press.

[297] Korn EL, Freidlin B. Conditional power calculations for clinical trials with historical controls. Stat Med. 2006;25:2922-31.

[298] Xiong X, M. T, J. B. A sequential procedure for monitoring clinical trials against historical controls. Stat Med. 2007;26:1497-511.

[299] Schoenfeld D. Sample-Size Formula for the Proportional-Hazards Regression Model. Biometrics. 1983;39:499-503.

[300] Hedeker D, Demirtas H, Mermelstein RJ. A mixed ordinal location scale model for analysis of Ecological Momentary Assessment (EMA) data. Stat Interface. 2009;2:391-401.

[301] Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999:496-509.

APPENDICES

Appendix I: Evaluation Schedules

Table 6.0.1 Evaluations at Baseline and Follow-up (Prior to Amendment 2.0)

Evaluations/Schedule[1]	Months after RT Start													
	0	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**42**	**48**	**54**	**60**
Imaging														
Diagnostic/Investigational MR	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MR Spine[4]	X			X			X			X		X		X
FDG PET[6]	X			X			X			X				
PET-methionine[6, 7]	X			X			X			X				
Lateral skull X-ray	X													
Bone Age/Q-CT/DEXA	X													
Clinical-Standard														
Assessment/Triage	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam‡#	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lab: CBC‡	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lab: Chemistry‡	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lab: Endocrine Screen‡	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Audiometry[2]‡	X			X			X			X		X		X
Endocrine Clinic‡	X			X			X			X		X		X
Neurology Clinic‡	X			X			X			X		X		X
Ophthalmology‡	X			X			X			X		X		X
CSF Cytology (Spinal tap)[5]	X													
Clinical-Investigational														
Endocrine/Provocative[3]	X			X			X							
Psychology	X			X			X			X		X		X
Function Laboratory	X			X			X			X		X		X
Sleep/Fatigue Research														
Actigraphy	X			X			X			X		X		X
Questionnaires/QOL	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory-Investigational														
Genomics	X													
Cytokines[7]	X			X			X			X		X		X

*Patient of childbearing potential requires a negative pregnancy test prior to starting treatment. (‡) should be repeated if clinically indicated following craniotomy. [1]Imaging and clinical tests should be performed prior to radiation therapy; however, logistics may make it difficult to complete all exams prior to treatment. The principal investigator reserves the right to accept pre-irradiation testing within 16 weeks of the initiation of radiation therapy. PET-FDG and PET-methionine will also be done at time of progression or recurrence if prior to 24 months. Assessment/triage includes neck and abdomen circumference. #Edinburgh Handedness Inventory performed once. [2]Patients who are unable to undergo standard audiometry may undergo ABR at the treating physician's discretion. [3]Provocative screening will not be conducted for patients when the number of days off corticosteroids prior to the test date is less than the number of days on corticosteroids prior to discontinuance.[4]MR spine may be performed more frequently for patients with spinal metastatic disease or at the discretion of the treating physician. [5]Lumbar

puncture for CSF cytology may be waived with PI approval based on contraindication or if adequate evaluation was performed within 3 weeks of enrollment. [6]METPET and FDG-PET scans not performed at 12, 24 or 36 month evaluation may be performed at a subsequent follow-up evaluation. All METPET studies will be whole-body regardless of the presence or absence of metastatic disease at the time of enrollment. [7]Test will not be collected after July 1, 2020

Table 6.0.2 Evaluations at Baseline and Follow-up at St. Jude (Amendment 2.0)

Evaluations/Schedule[1]		**Months after RT Start**															
	0	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27****	**30**	**33****	**36**	**42**	**48**	**54**	**60**
Imaging																	
Diagnostic/Investigational MR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MR Spine[4]	X				X				X				X		X		X
FDG-PET[6]	X				X				X				X				
PET-methionine[6, 9]	X				X				X				X				
Lateral skull X-ray	X																
Bone Age/Q-CT/DEXA[7]	X																
Clinical-Standard																	
Assessment/Triage	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam‡#	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lab: CBC‡	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lab: Chemistry‡	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lab: Endocrine Screen‡	X		X		X		X		X	X	X	X	X	X	X	X	X
Audiometry[2]‡	X				X				X				X		X		X
Endocrine Clinic‡	X				X				X				X		X		X
Neurology Clinic‡	X				X				X				X		X		X
Ophthalmology‡	X				X				X				X		X		X
CSF Cytology[5]	X																
Clinical-Investigational																	
Endocrine/Provocative[3]	X				X				X								
Psychology	X				X				X				X		X		X
Function Laboratory	X				X				X				X		X		X
Sleep/Fatigue Research																	
Actigraphy	X				X				X				X		X		X
Questionnaires/QOL	X	X	X	X	X	X	X	X	X		X		X	X	X	X	X
Laboratory-Investigational																	
Genomics	X																
Cytokines[8, 9]	X				X				X				X		X		X

*Patient of childbearing potential requires a negative pregnancy test prior to starting treatment. (‡) should be repeated if clinically indicated following craniotomy. [1]Imaging and clinical tests should be performed prior to radiation therapy; however, logistics may make it difficult to complete all exams prior to treatment. The principal investigator reserves the right to accept pre-irradiation testing within 16 weeks of the initiation of radiation therapy. PET-FDG and PET-methionine will also be done at time of progression or recurrence if prior to 24 months. Assessment/triage includes neck and abdomen circumference. #Edinburgh Handedness Inventory performed once. [2]Patients who are unable to undergo standard audiometry may undergo ABR at the treating physician's discretion. [3]Provocative screening will not be conducted for patients when the number of days off corticosteroids prior to the test date is less than the number of days on corticosteroids prior to discontinuance.[4]MR spine may be

performed more frequently for patients with spinal metastatic disease or at the discretion of the treating physician. [5]Lumbar puncture for CSF cytology may be waived with PI approval based on contraindication or if adequate evaluation was performed within 3 weeks of enrollment. [6]MET PET and FDG-PET scans not performed at 12, 24 or 36 month evaluation may be performed at a subsequent follow-up evaluation. All METPET studies will be whole-body regardless of the presence or absence of metastatic disease at the time of enrollment. [7]Patient must be > 3 years of age. [8]For patients enrolled before August 30, 2019 [9]Test will not be collected after July 1, 2020 **Optional at the dicretion of the treating physician

Appendix II: Evaluations During Radiation Therapy at St. Jude

TABLE 6.0.3 EVALUATIONS DURING RADIATION THERAPY

Evaluation	Week on therapy						
	1	2	3	4	5	6	7
Imaging							
Activation PET*	X	X	X	X	X	X	X
Clinical-Standard							
Physical examination	X	X	X	X	X	X	X
CBC			X				
Chemistry			X				
Clinical-Investigational							
QOL			X			X	
Toxicity Assessment	X	X	X	X	X	X	X
Laboratory-Investigational							
Cytokines[1]			X			X	

*frequency depending on feasibility and availability
[1]For patients enrolled before August 30, 2019

Appendix III: Research Tests

Prior to Amendment 2.0

Research Test	Time Acquisition
MRI of Brain	Baseline and 4, 8, 12, 16, 20, 24, 28, 32, 36, 42, 48, 54, 60 months
Sleep Fatigue and Quality of Life Questionnaires	Baseline, each week during treatment and 4, 8, 12, 16, 20, 24, 28, 32, 36, 42, 48, 54, 60 months
Serum Cytokine	Baseline, week 3 & 6 during treatment and 12, 24, 36, 48, 60 months
MET PET & FDG PET	Baseline and 12, 24, 36 month
Genomics	Baseline
Neuropsychological Testing	12, 24, 48, 60 months

Human Performance Laboratory	Baseline and 12, 24, 36, 48, 60 months
Actigraphy	Baseline and 12, 24, 36, 48, 60 months
Provocative Endocrine Testing	Baseline
Lateral skull X-ray	Baseline

Amendment 2.0

Research Test	Time Acquisition
MRI of Brain (research portion)	Baseline and 3, 6, 9, 12, 15, 18, 21, 24, 27 & 33 (optional), 30, 36, 42, 48, 54, 60 months
Sleep Fatigue and Quality of Life Questionnaires[1]	Baseline, each week during treatment and 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 42, 48, 54, 60 months
Serum Cytokine[1]	Baseline, week 3 & 6 during treatment and 12, 24, 36, 48, 60 months
MET PET[1] & FDG PET[1]	Baseline and 12, 24, 36 month
Genomics[1]	Baseline
Neuropsychological Testing	12, 24, 48, 60 months
Human Performance Laboratory[1]	Baseline and 12, 24, 36, 48, 60 months
Actigraphy[1]	Baseline and 12, 24, 36, 48, 60 months
Provocative Endocrine Testing[1]	Baseline
Lateral skull X-ray	Baseline
PET Activation[1]	Depending on feasibility and availability

[1]Performed only at St. Jude Children's Research Hospital. Collaborating sites will not participate in these tests.

Appendix IV: RERTEP Ophthalmology Form

Patient Name: MRN: Exam date:

Contrast Sensitivity		
	OD (Right Eye)	OS (Left Eye)
Circle one/eye	1 2 3 4 5	1 2 3 4 5
Legend	1=1.25%, 2=2.5%, 3=5%, 4=10%, 5=25%	

Visual Acuity		
	OD (Right Eye)	OS (Left Eye)
Distance Vision with Glasses		
Distance Vision without Glasses		
Near Vision With Glasses		
Near Vision without Glasses		
APD	+ / -	+ / -

Strabismus		
	OD (Right Eye)	OS (Left Eye)
XT	+ / -	+ / -
ET	+ / -	+ / -
HT	+ / -	+ / -

Visual Fields				
Method: ☐ Sitafast 24-2 ☐Goldmann ☐Confrontation				
Grade	Achievement	OD (Right Eye)	OS (Left Eye)	Descriptive
8	Monocular Full	+ / -	+ / -	
7	Monocular Quadrantic	+ / -	+ / -	
6	Binocular Quadrantic	+ / -	+ / -	
5	Monocular Hemianopic	+ / -	+ / -	
4	Binocular Hemianopic	+ / -	+ / -	
3	Monocular Hemi and Quadrantic	+ / -	+ / -	
2	Binocular Hemi and Quadrantic	+ / -	+ / -	
1	Total Loss	+ / -	+ / -	

Color Vision			
Method: ☐ Ishihara's ☐Farnsworth			
Grade	Colors Matched	OD (Right Eye)	OS (Left Eye)
8	Match 13-16 colors		
7	Match 11-12 colors		
6	Match 9-10 colors		
5	Match 7-8 colors		
4	Match 5-6 colors		
3	Match 3-4 colors		
2	Match 1-2 colors		
1	0 color matched		

Fundoscopy		
	OD (Right Eye)	OS (Left Eye)
Optic Atrophy		
Papilledema		

Other:_____

_____
Signature