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CHILDREN'S ONCOLOGY GROUP

ACNS0121

A PHASE II TRIAL OF CONFORMAL RADIATION THERAPY FOR PEDIATRIC PATIENTS WITH LOCALIZED EPENDYMOMA, CHEMOTHERAPY PRIOR TO SECOND SURGERY FOR INCOMPLETELY RESECTED EPENDYMOMA AND OBSERVATION FOR COMPLETELY RESECTED, DIFFERENTIATED, SUPRATENTORIAL EPENDYMOMA

An Intergroup Phase II Study for Participation by COG and the Dutch Childhood Oncology Group – SKION (Stichting Kinderoncologie Nederland)

Target Tumors
Ependymoma

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9/7/07

TABLE OF CONTENTS

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AGENT AND NSC#

Carboplatin (Paraplatin, CARBO)	NSC# 241240
Cyclophosphamide (Cytoxan, CPM)	NSC# 026271
Etoposide (Vepesid, ETOP)	NSC# 141540
Filgrastim (GCSF)	NSC# 614629
Mesna (MESNA)	NSC# 113891
Vincristine (Oncovin, VCR)	NSC# 067574

STATEMENT OF CONFIDENTIALITY

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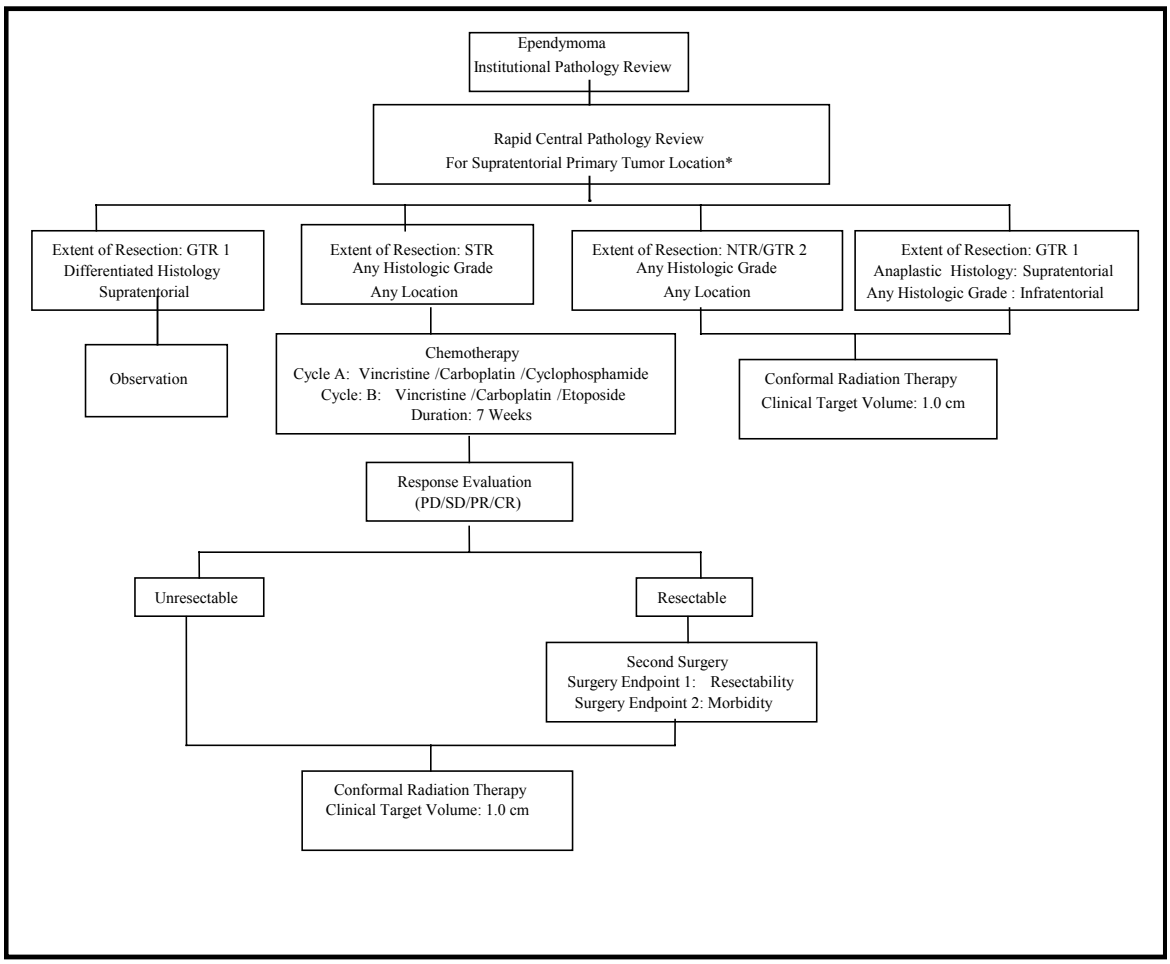
ABSTRACT

There is a need for a national treatment standard for all children with intracranial ependymoma. Ependymoma is a rare tumor, and with few exceptions, is seen relatively infrequently by the pediatric oncology community. Important questions to be answered with the aim of improving outcome for these children can be achieved by conducting a multi-institution study with the support of the Children's Oncology Group. Local control is the primary treatment objective for the proposed study because local failure is the predominant mode of failure. The local failure rate is highest among those patients who are classified as having had an incomplete resection despite the addition of postoperative radiation therapy. Currently available chemotherapy has failed to achieve an improvement in overall survival despite well-designed clinical trials to assess its usefulness. There has been a marked improvement in neurosurgical technique and radiation treatment technology. These two improvements are likely to impact significantly on the outcome for children with ependymoma by first increasing the rate of complete resection without added morbidity and secondly by reducing or eliminating many of the side effects attributable to radiation therapy in children. Additionally, potentially important prognostic variables such as age, histology, primary site location, and others need to be evaluated in the context of a contemporary clinical trial. There is variability in the expertise available to treat patients with ependymoma using the latest neurosurgery and radiation therapy treatment technology. At the biannual cooperative group meetings held from 1999 through 2001 to discuss childhood ependymoma, support was garnered among investigators to pursue the use of advanced technology at the majority of centers. Through the design and implementation of the proposed treatment trial it should be possible to safely increase the rate of complete resection and systematically deliver radiation therapy that is safer and more effective. This study proposes a 7 week course of chemotherapy using carboplatin, cyclophosphamide, etoposide and vincristine in children with incomplete resection prior to second surgery, conformal radiation therapy for all patients, and a trial of observation for completely resected supratentorial, differentiated ependymoma.

EXPERIMENTAL DESIGN SCHEMA



* - If extent of resection is indeterminant, rapid central pathology review cannot be performed, or tumor grade is indeterminant, the patient will receive conformal radiation therapy.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1
Estimate the local control and pattern of failure for completely resected, differentiated, supratentorial localized ependymoma after surgery alone.

1.2
Estimate the rate of complete resection with second surgery after chemotherapy for initially incompletely resected localized ependymoma.

1.3
Estimate the local control and pattern of failure for pediatric patients with localized ependymoma treated with 3-dimensional conformal radiation therapy using an anatomically defined 1.0-cm clinical target volume.

1.4
Determine the influence of histologic grade on the time to progression after conformal radiation therapy.

1.5
Determine (a) the chromosomal gains and losses in ependymoma by comparative genomic hybridization (CGH) using snap frozen and paraffin embedded tissue and (b) the mutation status of the INI 1 gene in tumors with deletions of 22q11.2 or any identified candidate tumor gene.

1.5.1
Using the Affymetrix SNP chip, determine the genome-wide allelotypes as well as patterns of chromosomal gains and losses in ependymoma

1.5.2
Integrate allelotyping and CGH data to refine genomic profiles of ependymoma.

1.5.3
Develop a molecular classification system for ependymoma based on genomic profiles (chromosomal aberrations) and expression profiles.

2.0 BACKGROUND

2.1 General Background

Ependymoma accounts for 8-10% of all childhood CNS tumors with fewer than 170 new cases diagnosed in the United States each year in children and adults less than age 25 years.[1] The mean age at diagnosis ranges from 51-71 months,[2-5] and 25 to 40% are diagnosed in children less than 3 years of age.[6] Survival statistics for ependymoma are generally disappointing with 5-year survival and progression-free survival estimates of 50-64% and 23-45%, respectively.[2,4,7-9] Recurrences are typically local with a median time to recurrence of 13-25 months;[2-4,7,8,10] 20% of failures have isolated distant recurrence. Late recurrences are not uncommon.

The standard of care for ependymoma is surgical resection compatible with an acceptable neurologic outcome followed by post-operative radiation therapy directed at the primary site. For very young children (age < 3 years), immediate post-operative irradiation is not widely accepted and multi-agent chemotherapy has been given in an effort to delay or avoid irradiation. There are no data to suggest an

obvious role for chemotherapy for patients with ependymoma, especially those greater than 3 years of age at the time of presentation. The poor outcome for children less than 3 years of age[11] has been attributed in part to the delay in the administration of radiation therapy, which suggests that the approach for this important group of patients with ependymoma should be re-evaluated.

2.2 Rationale for Surgery

Surgical resection appears to be the most important prognostic factor for children with ependymoma.[2-5,7-10,12,13] Patients with complete resection and radiation therapy have a 5-year survival estimate of 67-80% and a 5-year progression-free survival estimate of 51-75%, compared to a 5 year survival estimate of 22-47% and progression free survival estimate of 0-26% for patients with incompletely resected tumors treated with radiation therapy. Even though complete resection is considered instrumental for long-term event-free and overall survival, complete resection is achieved only for 42 to 62% of patients.[4,5,7,9] Complete resection is more easily achieved for tumors in supratentorial locations and from the roof of the fourth ventricle; tumors in other locations including those intimately associated with the lower cranial nerves have more morbidity associated with aggressive attempts at resection. Despite the high rate of incomplete resection after the initial surgery, few studies have used second surgery for patients with residual disease.[14,15] The timing of this surgery is of debate, and some favor the use of chemotherapy between the initial surgery and second surgery. The purpose of chemotherapy prior to second surgery is to make the tumor more amenable to resection while at the same time preventing tumor progression during the interval between procedures. Foreman et al.[14] performed second surgery on 5 patients with fourth ventricle tumors who had residual disease following the initial surgery. One patient had an immediate "second-look" surgery while the other four had short courses of chemotherapy prior to the second look surgery. A gross total resection was achieved in 4 of the 5 patients, 3 of whom received "sandwich" chemotherapy. No major morbidity was seen after second surgery; 3 of these 4 patients remained progression free at 23, 25 and 34 months after second surgery and post-operative radiation therapy.

Second resection has been systematically performed prior to radiation therapy at St. Jude Children's Research Hospital (SJCRH). From April 1997 through April 2000, 40 children were referred to SJCRH for treatment of intracranial ependymoma.[16] Twenty-four of 40 (60%) were considered to have a complete resection; the remaining 16 patients (40%) had residual tumor after initial attempts at resection. Twelve of the 16 patients were found to be candidates for additional resection based on the location of the residual tumor, neurologic status at the time of evaluation, and other clinical parameters. Complete resection was achieved in 10 of 12 patients undergoing second surgery. Combining the patients with complete resection after an initial resection with those who had complete resection after a second surgery increased the rate of complete resection for the entire group to 85%. The operative morbidity of the patients was low; significant morbidity, (gastrostomy or tracheostomy) occurred in 4 of 24 initially completely resected patients and 4 of 16 initially incompletely resected patients prior to second surgery. The additional surgery resulted in gastrostomy for one patient. Six of the twelve patients undergoing second surgery had progressed on chemotherapy prior to second surgery, which was given in an effort to delay radiation therapy. There have been isolated reports of successful treatment of newly diagnosed or recurrent intracranial ependymoma by resection alone.[17,18] Hukin et al.[17] reported 10 pediatric cases of intracranial ependymoma (8 supratentorial and 2 posterior fossa) who had gross total resection as the only initial therapy; 7 remain free of disease without further intervention at a median follow-up of 48 months. Three patients recurred at 20, 9 and 10 months following resection suggesting that there is a subgroup of patients with supratentorial intracranial ependymoma who might require only surgery, thus reserving radiation therapy and the potential for late effects for the time of recurrence.

Although a prospective trial has not been conducted to determine if observation is appropriate for any patient with ependymoma, observation after resection has been empirically recommended by some groups making this option a point of controversy that should be resolved in a cooperative group trial. Rogers et al.[19] showed in a contemporary retrospective review with 40 subjects, comparing the practices of two surgeons, that patients with posterior fossa ependymoma treated with gross-total resection and observation had an inferior 5 year actuarial local control and 10 year overall survival rate when compared to gross-total resection and irradiation (76.9% vs 100%, p=0.03) and (54.7% vs 85.7%, p=0.01), respectively.

2.3 Rationale for Conformal Radiation Therapy

Conformal radiation therapy may be used to increase the dose to the primary site and at the same time decrease the side effects of treatment. Reducing the dose of radiation administered to normal tissue is a logical approach for treating childhood ependymoma, but requires systematic evaluation and planning, treatment-failure monitoring and assessment of CNS effects. Merchant et al.[20] reported the preliminary results of a St. Jude Children's Research Hospital protocol (RT-1) that treated 64 pediatric patients with localized ependymoma after July 1997. This study used conformal radiotherapy with an anatomically defined clinical target volume margin of 1.0 cm surrounding the postoperative residual tumor and tumor bed. Only six failures occurred after a median follow-up period of 17 months (range, 3 to 43 months). The group included very young children with a median age of 3.0 years (range: 1.1 to 22.9 years). Both failures were encompassed by the prescription isodose. The majority of patients received a total dose of 59.4 Gy. Although the results of this trial await longer follow-up, the preliminary results are promising and suggest that the volume of irradiation may be substantially reduced without compromising disease control in pediatric patients with ependymoma.

2.4 Rationale for Chemotherapy

As noted earlier, the role of chemotherapy for intracranial ependymoma is uncertain. Multiple retrospective reviews have assessed the role of chemotherapy in newly diagnosed ependymoma and none has found chemotherapy to improve survival.[2-5,7,21,22] The Children's Cancer Group (CCG 942) compared radiation alone versus radiation and chemotherapy in children aged 2-16 years with ependymoma. This study concluded that adjuvant chemotherapy with lomustine, vincristine and prednisone did not improve outcome.[6] Another CCG study (CCG 921), a prospective randomized study of radiation therapy followed by lomustine, vincristine and prednisone versus "8 in 1", also showed no role for chemotherapy with survival statistics on either regimen no different than historical controls.[8]

Ependymoma has been shown to be responsive to certain chemotherapeutic regimens. Data from single agent phase II studies in recurrent ependymoma have been disappointing. Cisplatin, an ototoxic agent, has the highest response rate of 30%.[23] The phase II data by Gaynon et al.[24] support the use of carboplatin for patients with ependymoma. Their study showed a 40% overall response rate for patients with ependymoma who had not been previously treated with cisplatin. One of the principle reasons for using carboplatin is to avoid oto-toxicity. And while it may be true that 1-2 courses of cisplatin may have relatively less oto-toxicity than a longer more conventional course of cisplatin, there is a linear increase in the risk of significant and permanent hearing loss with each dose.[25]

Recent data using adjuvant combination chemotherapy in children with newly diagnosed ependymoma have shown encouraging responses. White et al. found an 86% response rate to 4 cycles of vincristine, etoposide and cytoxan in 7 children < 4 years of age with newly diagnosed ependymoma.[26] Mason et al. found a 16% response rate in 10 children < 6 years of age with newly diagnosed ependymoma treated with 4-5 cycles of cisplatin, vincristine, etoposide, and cytoxan.[27] In the POG infant study (POG8633), Duffner et al. demonstrated a 48% response rate to two cycles of vincristine and cytoxan in 25 infants less than 3 years of age with newly diagnosed ependymoma and also found that chemotherapy can allow for a

delay in radiation therapy by 1 year without decreasing survival.[11] Following the results obtained from the initial POG infant study (POG 8633), the successor study (POG 9233) compared standard (six 12 week cycles of cisplatin/cyclophosphamide/etoposide/vincristine) and dose-intensive (DI) chemotherapy (8 nine week cycles of the same chemotherapy with differences in relative intensity) for infants with brain tumors including ependymoma. There was a significant advantage in event-free survival for patients with ependymoma treated with (DI) chemotherapy although there was no difference in overall survival. The relative dose intensity differences were cisplatinum 1.67, cyclophosphamide 2.67, etoposide 1.54, and vincristine 1.33.[28] A recent prospective study by Needle et al.[10] used irradiation followed by carboplatin and vincristine alternating with ifosfamide and etoposide in patients greater than 36 months of age with newly diagnosed ependymoma. The 5 year progression free survival for the 10 patients with incompletely resected tumors was 80% and extent of surgical resection was not found to be of prognostic significance. These excellent survival statistics for incompletely resected ependymoma suggest that there may be a role for chemotherapy. Unfortunately, radiation therapy was not standardized and a portion of the patients received hyperfractionated radiation therapy, which confounds the analysis. The conclusion of these studies is that chemotherapy can have a response in ependymoma and may be able to delay the need for radiation, but thus far has not resulted in a survival advantage.

There exists the potential for chemotherapy to make residual tumor more amenable to complete surgical resection at the time of second surgery. Foreman et al. used chemotherapy between the initial and second surgery in 4 patients with ependymoma, enabling complete resection in 3 of the 4 patients, with all 3 progression free 23-34 months after second look surgery.[14] All patients showed viable tumor at the time of second surgery and the subjective impression by the neurosurgeon was that the tumors were better defined and easier to dissect following chemotherapy.

The role for chemotherapy in the present study would be to bridge the interval of time necessary to prepare the incompletely resected patient for a second surgery and to potentially make the tumor more amenable for resection. The mechanism by which chemotherapy makes a tumor easier to resect is unknown and probably is a combination of cytotoxic effects and anti-angiogenesis effects. Selection of the chemotherapy agents, delivery schedule and duration of treatment necessary to achieve these aims is difficult given the range of responses, differences in toxicity profiles, and lack of data from which to model such a study. No study has shown that the intensity of chemotherapy nor the response to chemotherapy correlate with the ease of resection at second surgery. Therefore, the chemotherapy regimen in this study will utilize a combination of the agents (vincristine, cytoxan, etoposide and carboplatin) which have shown the best response in ependymoma, and the dosing and schedule of administration has been chosen to limit toxicity. Only two cycles of chemotherapy (cycle A and B) will be given over a period of 7-8 weeks between the first and second surgery. This will to allow time to prepare for the second surgery and potentially change the nature of the tumor to make it more easily resected, but will not cause excessive delay in the definitive radiation. Carboplatin will be used rather than cisplatin to decrease the risk of ototoxicity. Cycle A will utilize vincristine, carboplatin and cytoxan at standard combination doses and GCSF will be given to speed the recovery of neutrophils. Cycle B will utilize vincristine, carboplatin and oral etoposide patterned off the schedule used in adults with nonsmall cell lung cancer.[29] Etoposide will be given on an extended oral schedule because there is data to suggest that some tumors, particularly slower growing tumors, respond better to prolonged exposure to chemotherapeutic agents. Needle et al. [30] demonstrated activity of oral etoposide in small number of patients with ependymoma; 2 of 5 responded including one who achieved a complete response.

2.5 Rationale for Histologic Grade in Treatment Stratification

Although the influence of histologic grade on outcome remains controversial, a number of recent studies have suggested that this factor may influence outcome.[12,31-37] Merchant et al.[37] recently reported from a contemporary series of 50 patients undergoing a blinded pathology review that histologic grade significantly influenced progression-free survival after irradiation ($p<0.001$). The estimated 2-year event-free survival was 32% $\pm$ 14% for patients with anaplastic ependymoma compared to 84% $\pm$ 7% for patients with differentiated ependymoma.

2.6 Rationale for Correlative Biological Studies and Molecular Classification of Ependymoma by CGH

There are no reliable biological prognostic markers for ependymoma. The role of histologic subtype in prognostication remains controversial despite numerous reports of small series of patients, reflecting our inadequate understanding of the biology of this tumor. We propose to use a comprehensive genetic approach to create a molecular classification for ependymoma and to identify the genetic alterations underlying the biological and clinical behavior of various subsets of this tumor. Although various techniques are available for such studies, some require either live cells (e.g. spectral karyotyping) or fresh frozen tissues (gene expression profiling), which are less feasible in a cooperative study setting. We have chosen a more robust technique, comparative genomic hybridization (CGH) for this purpose.[38,39] This technique involves labeling tumor DNA and normal DNA with different fluorescent markers and hybridizing them simultaneously to normal metaphase spreads. Based on the relative intensities between two fluorescent colors, regions of chromosome with relative gain or loss can be identified in a single hybridization. One advantage of CGH is the ability to use archival (paraffin embedded) materials when frozen tissues are not available, thus greatly expanding the number of cases that can be analyzed. Using the same technique, Feuerstein et al.[40] have analyzed a total of 44 cases of ependymoma (24 intracranial and 20 spinal cord) from pediatric and adult patients. Frequent chromosomal aberrations were found in intracranial tumors including gain of 1q and losses of 6q, 9 and 13. Gain on chromosome 7 was found almost exclusively in spinal cord tumors and was associated with various other chromosomal aberrations. The cytogenetic aberrations found in the 17 intracranial tumors from patients >3 years of age were different from those found in younger patients. These tumors had frequent gain of 1q (7 cases) and losses on 6 (6 cases), 9 (6 cases), 13 (4 cases) and X (3 cases). These pilot data suggest that cytogenetic aberrations differ in younger and older patients and may underlie age-related differences in outcome. In addition, these preliminary results are consistent with the idea that grade is associated with particular chromosomal numeric alterations. Gain of 1q and loss of 9 and 13 were preferentially associated with histologic grade 3 (5 of 7 cases, 6 of 6 cases, and 3 of 4 cases, respectively) among intracranial tumors. If subjectivity in grading underlies an inability to correlate grade and outcome in intracranial ependymoma, we might find that chromosomal abnormalities correlating with higher grade are indicators of outcome. These preliminary results are consistent with other reports involving smaller series[41-47] and suggest that categorizing ependymoma by cytogenetic aberrations may help establish a classification system that predicts the biological behavior of these tumors. A prospective ependymoma study with a large number of cases with outcome data will validate the existence of the groups we have identified in our pilot study and determine their clinical significance. Furthermore, this type of comprehensive cytogenetic analysis, when combined with other published observations such as the loss of chromosome 22q[47-52] and possible involvement of tumor suppressor genes such as NF2 or INI1 may provide important leads to clinically relevant genes involved in the initiation and progression of these tumors.

The standard format of CGH has limited resolution (~ 10-15 megabases) because of its dependence on the morphology of metaphase chromosomes. Extensive follow-up work is required to identify candidate genes after regions of gain or loss have been identified. To overcome these limitations, a modification of CGH to an array format has been developed. For detecting gains and losses, array CGH replaces normal metaphase spreads with a series of selected human genomic DNA fragments 100-200 kilobases that are

packaged in replicable units called bacterial artificial chromosomes (BACs). These BAC's are selected such that they are distributed every 1-2 megabases throughout the chromosomes and together represent the entire genome. BACS have been spotted onto glass slides in an array and initial results comparing chromosomal and array CGH show a high rate of concordance between the two techniques. This high throughput and more sensitive array format will greatly improve the precision and efficiency of CGH, produce a precise physical map of the genetic abnormalities and analyze more samples in less time. As a companion to the objectives of this study, complete genetic profiles of all patients will be generated by array CGH after this technique has been validated using chromosomal CGH as a gold standard. The profiles will be analyzed for relationships with age at diagnosis, location of tumor, histology, response to therapy and long term outcome.

Parallel studies using cDNA microarrays will also be conducted to generate gene expression profiles to complement array CGH studies whenever snap frozen tissues are available. Recent reports have demonstrated the feasibility of molecular classification of cancer by expression profiling.[53,54] We hypothesize that combining both genetic and expression profiles will increase our ability to subclassify ependymoma. Our ultimate goal is to build a molecular classification system for ependymoma to allow objective patient stratification for future clinical trials. In addition, identifying the genetic abnormalities in ependymoma may ultimately lead to the discovery of new therapeutic targets.

Because the INI1 gene has been found to be involved in a majority of atypical teratoid rhabdoid tumors (ATRT) and is located in 22q11.2, our plan is to examine the mutation status of INI1 in all ependymoma cases that have deletions involving the 22q11 region. Similar approaches will also be used to follow-up on recurrent regions of copy number changes in order to identify candidate genes that may play a role in the pathogenesis of ependymoma and its biological behavior.

At the outset of this study, we proposed to establish a molecular classification system for ependymoma based on genomic profiling as well as gene expression profiling. We outlined the use of molecular cytogenetic techniques such as array-based comparative genomic hybridization (aCGH) to perform genomic profiling. We recognized that CGH could not detect loss of heterozygosity (LOH) in the situation where there is no net loss such as loss of one allele followed by reduplication. We tried a number of methods to accomplish genome-wide allelotyping to complement the CGH results but were hampered by either low resolution using microsatellite markers or prohibitive cost of the various single nucleotide polymorphism (SNP) platforms. Recent developments by Affymetrix and other companies have resulted in significant improvement in their high-density SNP array and parallel genotyping of over 500K SNPs using a one-primer assay is now feasible at an affordable price.[55] The current Affymetrix 500K SNP array set is comprised of two arrays, each capable of genotyping on average 250,000 SNPs. One array uses the Nsp I restriction enzyme (~262,000 SNPs), while the second uses Sty I (~238,000 SNPs). The median physical distance between SNPs is 2.5 kb and the average distance between SNPs is 5.8 kb. The average heterozygosity of these SNPs is 0.30. This provides a great tool to perform genome wide LOH profiling. We have recently optimized the use of the 250K SNP array (the Sty I arrays in the 500K set) for both LOH and CGH studies using whole genome amplified DNA. Our results showed that we could obtain accurate and reproducible genomic profiles using as little as 10 ng of DNA as starting material and that both LOH data and CGH data can be obtained simultaneously in one hybridization experiment.

Because we will be generating array CGH and expression profiles of ependymoma samples from this protocol, it would be logical if we could complete the genomic profiling using the SNP chip as a complementary technique. Our preliminary results from integrating genomic profiles from different technology platforms have revealed prognostically significant genes that were not detectable by analyzing either type of profiling data alone. In a recently published report,[56] we evaluated the reliability of using

whole genome amplified DNA for analysis with an oligonucleotide array that contains 11,560 SNPs to detect allelic imbalance - LOH, chromosomal gain, loss or amplification. Independently, Zhao et al also reported similar findings.[57] In our study, whole genome SNP analysis were performed with DNA extracted from both osteosarcoma tissues and the corresponding patient-matched blood samples. SNP calls were performed by GeneChip® DNA Analysis Software. Our results indicate that SNP calls generated with amplified DNA are comparable to unamplified DNA. With unamplified DNA, 793 and 1070 SNPs were found to have LOH in the each of two osteosarcomas respectively. The use of whole genome amplified DNA was able to detect 78 and 83% of these SNPs with LOH from unamplified DNA with an average false positive rate of 13.5. Furthermore, using the Affymetrix GeneChip® Chromosome Copy Number Tool to analyze SNP array data, we were also able to detect chromosomal regions of gain, loss and amplification with amplified DNA from osteosarcoma. Recently, we also used the CNAG (Copy Number Analyser for GeneChip®) software to refine the copy number calls from the 250K SNP array data.

Since we are already doing array CGH with the DNA extracted from the tumor tissues and blood is collected for this protocol, we could make use of the same DNA preparations from the tumors and blood for SNP allelotyping. Thus this will not create any additional request for tissues but will greatly enhance the robustness and reliability of the molecular signatures that will be generated from these genomic studies.

2.7 Gender and Race Differences

There is no reported evidence to suggest that there are differences in outcome by gender or race when otherwise identical patients receive the same treatment.

3.0 STUDY ENROLLMENT AND PATIENT ELIGIBILITY

Important Note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.

3.1 Timing Of Enrollment And Start Of Treatment

3.1.1
Patients must be enrolled on study within 56 days of initial surgical resection at which time tissue is acquired to determine a diagnosis. Enrollment > 56 days after initial surgery will require written consent by the study chair.

3.1.2
Patients must be enrolled before treatment begins (patients receiving chemotherapy or radiation therapy must be enrolled prior to start of these therapies). The date protocol therapy is projected to start must be no later than 21 days after the date of study enrollment.

3.2 Patient Status

3.2.1 Age
Patients must be > 12 months and < 21 years at the time of enrollment.

3.2.2 Diagnosis
Histologically confirmed intracranial ependymoma. Patients with differentiated ependymoma (WHO II) or anaplastic ependymoma (WHO III) are eligible as are various subtypes described as clear cell, papillary, cellular or a combination of the above. Patients with primary spinal cord ependymoma, myxopapillary ependymoma, subependymoma, ependymoblastoma or mixed gliomas are not eligible.

3.2.3 Mandatory Submission of Tissue for Central Pathology Review (See Section 13.0)
All patients must have central pathology review. Pathology slides from the time of diagnosis must be sent to the COG Biopathology Center within 5 days of study enrollment. Failure to send pathology slides will make the patient ineligible.

Patients with a supratentorial primary site must have RAPID CENTRAL PATHOLOGY REVIEW. Pathology slides must marked RAPID REVIEW and submitted by overnight express to the Biopathology Center (See Section 13.0 for information regarding specimen submission).

3.2.4 Mandatory Submission of Imaging Studies for Central Review (See Section 10.5).
This includes pre-and post-operative brain and spine MR submitted to Quality Assurance Review Center (QARC) to confirm eligibility for the study.

3.2.5 Extent of Disease
No evidence of non-contiguous spread beyond the primary site as determined by pre of post-operative MR imaging of brain, pre or post-operative MR imaging of the spine and pre and pre or post-operative CSF cytology obtained from the lumbar CSF space (the requirement for lumbar CSF examination may be waived if deemed to be medically contraindicated). CSF cytology from a ventriculostomy or permanent VP shunt that reveals the presence of tumor cells is indicative of metastatic disease.

3.2.6 Performance Level
There is no minimum performance level. Children with ependymoma may suffer neurologic sequelae as a result of their tumor or surgical measures taken to establish a diagnosis and resect the tumor. In the majority of cases there is neurologic recovery. Neurologic recovery is not likely to be impeded by protocol therapy.

3.3 Prior Therapy

3.3.1
No prior treatment other than surgical intervention and corticosteroids. Patients who have had more than one surgery will be eligible. Corticosteroid therapy is permissible.

3.3.2
Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary (See Section 5). There is no minimum hemoglobin level during radiation therapy.

3.4 Exclusion Criteria

3.4.1
Patients who are unable to undergo MR imaging (*i.e.,* MR incompatible vascular clips).

3.4.2
Patients who are pregnant or breast feeding will not be eligible. Patients of childbearing potential must practice an effective method of birth control while participating on this study.

3.5 Regulatory

3.5.1
All patients and/or their parents or legal guardians must sign a written informed consent prior to study enrollment.

3.5.2
All institutional, FDA, and NCI requirements for human studies must be met.

3.6 Study Enrollment

3.6.1 IRB Approval
Upon receipt of local IRB approval for a COG study, fax the officially signed IRB approval to the Group Operations Center (GOC) at: (626) 445-6715. The *COG IRB Approval Fax Cover Sheet* is required to be faxed with the official approval. A copy of this cover memo can be obtained from the protocol links area of the COG website. After this approval is recorded by GOC staff, the institution will have access to the eRDE enrollment screens.

3.6.2 Patient Registration
Prior to study enrollment, all patients must have been registered via the eRDE system into the COG Cancer Registry (Diagnosis/Registry). The patient registration application is available 24 hours a day, 7 days a week. The assigned COG patient identification number will be used to identify the patient in all future interactions with the COG. If you have problems with registration, please refer to the online help in the eRDE area of the COG website.

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID. Please use this number as part of the labeling information on all banking and biology specimens sent to the Biopathology Center or a COG Reference Laboratory. If you have a question about a patient's BPC Number, please call the Biopathology Center at (800) 347-2486.

3.6.3 Study Enrollment
Patients may be enrolled on the study once all eligibility requirements for the study have been met. Study enrollment is accomplished by going to the Enrollment application in the eRDE system. If you have problems with enrollment, refer to the online help in the Applications area of the COG website.

4.0 TREATMENT PROGRAM

Once a patient has been determined to be eligible for protocol treatment, the sequence of treatment will be based on extent of resection prior to enrollment, tumor location and histologic grade. (See Study Design Schema).

4.1 Surgery and Extent of Resection Guidelines

Guidelines to define the extent of resection at the time of enrollment are critical to the performance of this trial. Patients are allowed to have had more than one attempt at resection prior to enrollment. Extent of resection may be classified for purposes of therapy and analysis as follows:

4.1.1 GTR1 (Gross Total Resection 1)

No visible residual tumor identified with the operating microscope and no evidence of disease on post-operative neuroimaging.

4.1.2 GTR2 (Gross Total Resection 2)

Microscopically visible residual tumor identified with the operating microscope and no evidence of disease on post-operative neuroimaging.

4.1.3 NTR (Near Total Resection)

Residual tumor evident on post-operative neuroimaging with thickness or nodularity measuring less than or equal to 5 mm in greatest dimension. Linear "streak" enhancement or signal intensity changes are not included in the measurement of residual to determine near-total versus sub-total resection.

4.1.4 STR (Subtotal Resection)

Residual tumor on post-operative imaging measuring greater than 5mm in nodularity or thickness. The definition of STR includes any surgical intervention that removes tissue that may be documented by pathology as tumor. A biopsy is an STR. More information is available in Section 4.2.3.

4.2 Treatment Plan By Extent of Resection at Time of Enrollment (See Experimental Design Schema)

4.2.1 Supratentorial Anaplastic Ependymoma (GTR1, GTR2, NTR) and Anaplastic or Differentiated Infratentorial Ependymoma (GTR1, GTR2, NTR) and Supratentorial Differentiated Ependymoma (GTR2, NTR)

Patients will receive conformal radiation therapy directed at the primary site using an anatomically defined clinical target volume 1.0 cm beyond the gross tumor volume.

4.2.2 Gross Total Resection Supratentorial Differentiated Ependymoma (GTR1)

Patients will be observed provided that rapid central pathology review (See Section 13.2) confirms the diagnosis of differentiated ependymoma and post-operative neuroimaging confirms that there is no evidence of disease. The operating neurosurgeon should explicitly state in the written operative report that no visible microscopic disease was apparent through the operating microscope.

Under the condition that the extent of resection is indeterminate because the surgeon cannot unequivocally report that microscopic disease is not present, or rapid central pathology review cannot be performed, or the information necessary to determine extent of resection at the time of the operation is not available, the patient will receive conformal radiation therapy. For those patients who are enrolled on this treatment arm and experience recurrence, they may then undergo additional surgery if feasible and be

treated according to the protocol-specified guidelines omitting the observation arm provided there is no metastatic disease (See Section 4.3.2). Data from the treatment and follow-up of these patients will remain part of this study.

4.2.3 Sub-Total Resection Any Histology or Location (STR)

Patients will receive chemotherapy prior to second surgery. At the completion of two courses of chemotherapy, the patient will undergo evaluation for second surgery. The evaluation will be used to determine the response to chemotherapy and the possibility of second resection. Second resection following completion of chemotherapy should be performed within 30 days after the completion of chemotherapy (i.e., before day 52 of cycle B of chemotherapy) if deemed safely feasible by the institutional neurosurgeon. Patients clearly not eligible for second surgery should proceed directly to conformal radiation therapy within the same time frame. Patients who achieve a CR to chemotherapy will not undergo second surgery and should proceed directly to conformal radiation therapy within 30 days. Patients who undergo second surgery should begin conformal radiation therapy within 30 days after second surgery. If radiation therapy is delayed beyond 30 days, please notify the Study Chair. The extent of resection and morbidity of second surgery will be assessed. There is no limit to the number of surgical procedures performed after chemotherapy and prior to radiation therapy.

While it is true that one might foresee a situation in which a patient, assessed after their initial surgery would not appear to be a candidate for second surgery due to tumor location or complications, the final decision about second resection should be reserved until after chemotherapy has been completed. After the initial surgery and during the time period for which the chemotherapy has been planned, normal brain has a tendency to shift and reposition itself into a more natural configuration. In addition, during the same time period, the appearance and extent of the residual tumor might become clearer, which could influence decisions about second surgery. For those children who may have suffered severe neurologic complications after their initial surgery, significant recovery is possible during the chemotherapy phase of the study. For this reason performance status has been omitted as one of the eligibility requirements. The basic premise of this study is to perform second surgery. Hopefully chemotherapy will intrinsically improve the ability to achieve minimal residual tumor with second surgery. The use of chemotherapy will also be successful if it only serves as a means to delay the decision to perform the second surgery and allows those children, who would otherwise have been referred for radiation therapy with residual disease to undergo a second resection. The use of chemotherapy and second surgery in this protocol should not be considered as justification for performance of surgery only to establish a diagnosis and not attempt to resect or debulk tumor and alleviate symptoms.

When it has been determined by the primary oncology team that chemotherapy or second surgery for a patient with residual tumor in the STR category would not be in the best interest of the patient, they may proceed with radiation therapy after contacting the study chair.

4.3 Observation Patients (GTR1) and the Observation Arm

4.3.1

The statistical design of the study includes interim monitoring of the cohort of patients who will be observed after surgery (4.2.2 and 14.4.4). In the event that the progression-free survival is determined to be inadequate, this arm of the trial will be closed and all children with GTR1, regardless of histologic grade, will receive post-operative conformal irradiation in the same manner as those patients included in section 4.2.1.

4.3.2

Patients who have local recurrence after surgery and observation (4.2.2) may receive treatment on this study provided they fulfill the eligibility requirements (excluding eligibility requirement 3.1.1). They will be treated according to the protocol schema omitting the observation arm. At the time of recurrence after surgery and observation, the child may be treated with surgery or chemotherapy as the first therapy after recurrence. Based on the extent of resection, when applicable, the child may receive chemotherapy on protocol or proceed with irradiation.

4.4 Chemotherapy

Patients whose extent of resection is characterized as STR at the time of protocol entry will receive 2 cycles of chemotherapy as outlined below. Chemotherapy should begin within 21 days following study enrollment. Patients will receive one cycle of cycle A (vincristine, carboplatin, cyclophosphamide) and one cycle of cycle B (vincristine, carboplatin, oral etoposide). The entire length of the chemotherapy phase is 7 weeks unless delay occurs due to myelosuppression or unanticipated toxicity. After patients have completed the chemotherapy phase, MR of the brain should be performed (3-5 weeks after the start of cycle B) to evaluate the feasibility of second surgery. Patients experiencing local tumor progression during the chemotherapy phase should discontinue chemotherapy and proceed to second surgery whenever possible followed by conformal radiation therapy. **Progressive disease during chemotherapy should be reported to the study chair.** Locally progressive disease during chemotherapy does not remove the patient from further protocol therapy. Evidence of dissemination beyond the primary site during the chemotherapy phase will remove the patient from protocol therapy.

Each cycle of chemotherapy will begin when the ANC>750/μl and platelets >75,000/μl and off filgrastim for at least 48 hours.

CHEMOTHERAPY SCHEMA

		Cycle A			Cycle B			
Week		0	1	2	3	4	5	6
Day		1 2	8		1	8	15	22
Cycle A	Vincristine (1.5 mg/m^2/dose—IV)	X	X					
	Carboplatin (375 mg/m^2/day—IV)	X						
	Cyclophosphamide (1000 mg/m^2/dose—IV)	X X						
	Mesna (200mg/m^2/dose – IV)	X X						
	Filgrastim (5mcg/kg/day—SC or IV)		Daily until ANC>1500/μl					
Cycle B	Vincristine (1.5 mg/m^2/dose—IV)				X	X		
	Carboplatin (375 mg/m^2/day—IV)				X			
	Etoposide (50 mg/m^2/day - PO)				Daily days 1-21 (oral)			

4.4.1 Cycle A

Vincristine (1.5mg/m^2/day) (maximum dose 2 mg) Day 1 and 8 given as IV bolus. For patients with BSA<0.45m^2 the dose is 0.05mg/kg.

Carboplatin (375 mg/m^2/day) Day 1 given as an IV infusion over one hour. For patients with BSA < 0.45m^2 the dose is 12.5 mg/kg/day. Patients who have compromised renal function should undergo a GFR. If the GFR is < 100 ml/min/1.73m^2 the carboplatin dose should be modified according to Section 4.5.3.

Cyclophosphamide (1000mg/m^2/day) Day 1 and 2 given as an IV infusion over one hour following carboplatin administration. For patients with BSA<0.45m^2 the dose is 33mg/kg/day on Day 1 and 2. Hydrate with D5-1/2NS at a rate of 125cc/m^2/hour for at least 2 hours before cyclophosphamide and continue hydration at 125cc/m^2/hour for 3 hours after. Use lasix (0.5mg/kg) IV if urine output is less than 3cc/kg/hr.

Mesna (200mg/m^2/dose) Day 1 and 2. For patients with BSA<0.45m^2 the dose is (7mg/kg/dose). Combine mesna (200mg/m^2) with cyclophosphamide and administer intravenously over one hour followed by mesna (200mg/m^2) in 375 cc/m^2 D5-1/2NS and run intravenously over 3 hours at 125 cc/m^2/hr. After 3 hour mesna, administer mesna (200 mg/m^2/dose) IV over 15 minutes at hour 5.

Filgrastim (5mcg/kg/day) start on Day 3 and continue until ANC >1500/µl given subcutaneously or intravenously. Do not use substitutes for filgrastim.

4.4.2 Cycle B

Cycle B is to begin at week 3 (22 days after cycle A) or when ANC>750/µl (off filgrastim for at least 48 hours) and platelets>75,000/µl.

Vincristine (1.5mg/m^2/day) (maximum dose 2 mg) Day 1 and 8 given as IV bolus. For patients with BSA<0.45m^2 the dose is (0.05mg/kg).

Carboplatin (375 mg/m^2/day) Day 1 given as an IV infusion over one hour. For patients with BSA < 0.45m^2 the dose is 12.5 mg/kg/day. Patients who have compromised renal function should undergo a GFR. If the GFR is < 100 ml/min/1.73m^2 the carboplatin dose should be modified according to Section 4.5.3.

Etoposide (50 mg/m^2/day) orally once daily on Days 1 through 21. For patients with BSA < 0.45 m^2, the dosage is 1.7 mg/kg/day on Days 1 through 21. Etoposide is commercially available in two forms, capsules containing 50 mg and a parenteral solution which may be consumed orally containing 20 mg etoposide per ml. If the m^2 dosing results in a daily dose between 45 and 55 mg, a single 50 mg capsule may be taken. For patients where the dose falls out of this range or for patients unable to swallow the capsules, the parenteral formulation should be substituted. **A 1:1 dilution of parenteral etoposide mixed in preservative free normal saline (for a final concentration of 10mg/ml) is stable for 3 weeks in Burron plastic oral syringes stored at room temperature. The oral solution can be administered further diluted in juice prior to administration. It is recommended that individual oral syringes containing the calculated daily dose of etoposide be prepared for each patient. Do not seal this chemo with a hard plastic cap; etoposide will crack hard plastic.** Consult Section 7.3 as well as specialized oncology reference sources for further guidance regarding the packaging, administration and handling of etoposide by health professionals and patients.

Patients should have blood drawn Day 8 and 15 to check the CBC, differential and platelets. If ANC<500/µl or platelets<50,000/µl oral etoposide should be discontinued and not restarted.

4.5 Dose Modifications Based on Toxicity

4.5.1 Hematologic Toxicity

Each cycle is to begin when the ANC>750/µl and the platelets>75,000/µl and off filgrastim for at least 48 hours. If ANC or platelet count do not recover by Day 29 of any cycle call study chair. During cycle B, patients should have blood drawn day 8 and 15 to check the CBC, differential and platelets. If ANC<500/µl or platelets<50,000/µl oral etoposide should be discontinued prematurely.

4.5.2 Hepatotoxicity

If the total bilirubin is 1.5-1.9 mg/dl vincristine dose should be reduced by 33%. If the total bilirubin is >1.9 mg/dl vincristine should be held.

4.5.3 Nephrotoxicity

Patients who have compromised renal function should undergo a GFR. This includes patients with a creatinine > 0.6 mg/dL before or during chemotherapy or at any time that the creatinine increases to 1.5 times the patient's baseline creatinine during therapy. If the GFR is <100ml/min/1.73m^2, the carboplatin dose should be calculated per the modified calvert formula using a target AUC of 5. Modified calvert formula: [58]

Carboplatin dose (mg/dose) = target AUC x [GFR(ml/min) + (0.36 x BW (kg))].

Note: The Carboplatin Calvert Formula uses the "RAW" GFR and not the GFR that measures the patient's renal function.

The actual dose of carboplatin administered should be the lower of the calculated doses, i.e. dose per the modified calvert formula using an AUC of 5 versus 375 mg/m^2/day or 12.5 mg/kg/day for patients with BSA < 0.45m^2. If the GFR is < 50 ml/min/1.73m^2, carboplatin should be held.

4.5.4 Hematuria

Cyclophosphamide should be deleted for gross hematuria lasting more than 24 hours. For gross hematuria improving after 24 hours, cyclophosphamide does not need to be modified, but the dose of mesna should be increased to 360mg/m^2/dose (12mg/m^2/dose for patients with BSA<0.45m^2) and administer in the following manner. Combine mesna (360mg/m^2) with cyclophosphamide and administer intravenously over one hour, followed by mesna (360mg/m^2) in 375 cc/m^2 D5-1/2NS and run intravenously over 3 hours at 125 cc/m^2/hr. After 3 hour mesna, administer mesna (360 mg/m^2/dose) IV over 15 minutes or orally at hour 5, 8 and 11. Ensure adequate fluid hydration at 3000cc/m^2/day for 24 hours following the last dose of cyclophosphamide. No modification needed for microscopic hematuria.

4.5.5 Neurotoxicity

For seizure due to vincristine, the drug is held for one dose, then reinstituted at 50% dose after appropriate anticonvulsants are administered. If seizures do not recur, full dose may be resumed. For grade 3 or 4 peripheral neuropathy, hold one dose of vincristine and then reinstitute at 50% dose. If symptoms resolve, full doses of vincristine can be resumed.

4.5.6 Emesis

If vomiting occurs within 30 minutes of dosing etoposide, repeat the full dose.

5.0 SUPPORTIVE CARE GUIDELINES

5.1 Venous Access

For patients receiving chemotherapy, an indwelling central venous access catheter is recommended but optional to facilitate chemotherapy and the use of sedation/anesthesia in young children.

5.2 Antiemetics

Cyclophosphamide, carboplatin and radiation therapy may cause moderate to severe nausea and vomiting. Appropriate antiemetics should be administered prophylactically and as needed. Corticosteroid use as an antiemetic should be avoided if possible.

5.3 Filgrastim (G-CSF)

All patients receiving chemotherapy will be given Filgrastim following Cycle A. Filgrastim will begin on Day 3 of cycle A and will continue through the nadir. Filgrastim will be discontinued when the ANC is greater than 1500/μl.

5.4 Fever and Neutropenia

Patients who develop a fever greater than 38.5 °C should be evaluated for neutropenia and infection. If the patient has an indwelling catheter or has an ANC<500/μl blood cultures should be drawn and administration of antibiotics should be considered. Aminoglycosides should be avoided if possible to decrease the chance of ototoxicity.

5.5 Prophylactic Antibiotics

Patients who receive chemotherapy should be started on trimethoprim/sulfamethoxazole at 5mg/kg/day dosed 2-3x/week or per primary care institution's protocol for Pneumocystis carinii prophylaxis. TMP/SMZ can be discontinued 3 months after chemotherapy has discontinued. Patients with TMP/SMZ allergy should be considered for treatment with dapsone or inhalation pentamidine.

5.6 Blood Products

Packed red blood cells should be given for symptomatic anemia or Hgb < 6-7gm/dL. Platelets should be transfused for platelets < 10,000-30,000 dependent on the neurosurgeon's preference. All blood products should be irradiated to prevent GVHD. There is no minimum hemoglobin level during radiation therapy. During radiation therapy, patients should be treated symptomatically.

5.7 Hemorrhagic Cystitis

Cyclophosphamide will be administered with mesna and vigorous fluid hydration to help avoid hemorrhagic cystitis. Attempt to maintain a urine output of > 3 cc/kg/hour before cyclophosphamide and for the first 8-10 hours following administration of cyclophosphamide. See guidelines under **Dose Modification** for modification in mesna dosing and hydration if gross hematuria occurs.

5.8 Nutritional Support

Any patient with greater than 10% weight loss should begin nutritional supplementation or begin treatment with an appetite stimulant such as megace or marinol. Nutritional support can be provided by enteric feeding or parenteral hyperalimentation.

6.0 REQUIRED OBSERVATIONS

6.1 Required Observations Before and During Protocol Therapy

Observation	Prior to Study Entry	Prior to Pre-XRT Chemo	During Pre-XRT Chemo	Prior to Second Surgery	Following Second Surgery	Prior to XRT	During XRT
History and Physical	X		X (Weekly)	X	X		X (Weekly)
Neurologic Assessment	X			X	X		
Weight, Height and Occipitofrontal Circumference (OFC)	X		X (Weekly)	X			
MR Brain with gadolinium	X[3]	X[5]		X[3]	X[3]	X[10]	
MR Spine with gadolinium	X[4]			X			
Lumbar CSF Cytologic Evaluation [1]	X					X	
BUN, Serum Electrolytes		X	X[6]				
Serum Creatinine		X	X[6]				
Calcium, magnesium, phosphorus		X					
Sodium, Potassium			X[7]				
Liver Functions (ALT, Bili)		X	X[6]				
Urinalysis		X	X[6]				
CBC, Diff., Platelet Count		X	X (Weekly)[8]	X		X	X (Weekly)[11]
PT, PTT				X			
Audiogram or BAER		X		X		X	
Neuropsychologic Evaluation (See Section 12.0)							X[12]
Pathology and Biology Specimens (See Section 13.0)	X				X		
Ophthalmology Evaluation	X[14]						
Endocrine Evaluation[2]	X						
Pregnancy Test [13]	X						

1- Obtain unless lumbar puncture is contraindicated and deemed medically unsafe.
2 - Endocrine evaluation to include: (8 a.m. draw) cortisol, free T4, TSH, IGF-1 and IGF-BP_3.
3 - Obtain both pre and post surgery. Post-op should be done within 21 days following surgery, preferably within 72 hours.
4 - Obtain within 10 days prior to surgery or attempt to wait 10 days after surgery (with contrast).
5 - If post-op cranial MRI was performed >21 days before the first day of chemo, repeat cranial MRI with gadolinium to provide an appropriate baseline.
6 - Obtain on Day 1 of Cycle A and B. Repeat weekly if abnormal.
7 - Obtain on Day 1 and Day 2 of Cycle A.
8 - Obtain on Day 1 of Cycle A and B and weekly, may need to be checked more frequently during nadir.
9 - Obtain within 30 days after the start of Cycle B.
10 - Perform within 21 days of beginning radiation. (May be the same as the initial post-op or post-op after second surgery depending on the treatment stratum)
11 – Obtain for patients treated with chemotherapy.
12 - Obtain within 4 months of beginning RT. Evaluations performed between the time of diagnosis and start of therapy will be accepted.
13 - Obtain for females 13 years or older
14 – Prior to study enrollment is preferred although within 4 months of beginning RT is acceptable.

6.2 Required Observations For Supratentorial Differentiated Ependymoma GTR1 Patients (Observation)

Observation (Time measured from date of enrollment)	Prior to Study Entry	4 Months	8 Months	12 Months	16 Months	20 Months	24 Months	28 Months	32 Months	36 Months	42 Months	48 Months	54 Months	60 Months	Annually After 5 Years
History and Physical	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height, Weight and OFC	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurologic Assessment	X			X			X			X		X		X	X
MR Brain with gadolinium	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MR Spine [1]	X			X			X								
CSF Cytology [2]	X			X											
Audiogram or BAER	X	X		X			X			X		X		X	X
Ophthalmology Evaluation	X			X			X			X		X		X	X
Endocrine Evaluation [3]	X			X			X			X		X		X	X
Neuropsychometric Evaluation (See Section 12)		X[4]					X[5]					X[5]			

1 - Repeat if new symptoms develop
2 - Obtain unless lumber puncture is contraindicated and deemed medically unsafe
3 - Endocrine evaluation to include: (8 a.m. draw) cortisol, free T4, TSH, IGF-1 and IGF-BP_3
4 - Obtain within ± 4 months of enrollment.
5 – Obtain within $\pm$ 4 months of the specified time point.

6.3 Required Observations Following Protocol Therapy

Observations (Dated from Start of Radiation Therapy)	**4 Months**	**8 Months**	**12 Months**	**16 Months**	**20 Months**	**24 Months**	**28 Months**	**32 Months**	**36 Months**	**42 Months**	**48 Months**	**54 Months**	**60 Months**	**Annually After 5 Years**
History and Physical	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height , Weight and OFC	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MR Brain with gadolinium	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Neurologic Assessment			X			X			X		X		X	X
MR Spine [1] (with gadolinium)			X			X								
CSF Cytology[6]			X											
Serum Creatinine, BUN	X[3]		X[4]			X[4]			X[4]		X[4]		X[4]	X[4]
Liver Functions (ALT, Bili)	X[3]		X[4]			X[4]			X[4]		X[4]		X[4]	X[4]
CBC	X		X			X			X		X		X	X
Audiogram or BAER			X			X			X		X		X	X
Neuropsychometric Evaluation (See Section 12)						X[5]					X[5]			
Ophthalmology Evaluation			X			X			X		X		X	X
Endocrine Evaluation [2]			X			X			X		X		X	X

1 - Perform at the indicated time points and repeat if new symptoms develop
2 - Endocrine evaluation to include: (8 a.m. draw) cortisol, free T4, TSH, IGF-1 and IGF-BP_3
3 - Obtain for patients who had chemotherapy
4 - Obtain as indicated
5 – Obtain within +/- 4 months
6 – Obtain unless lumbar puncture is contraindicated and deemed medically unsafe.

7.0 DRUG INFORMATION

7.1 **CARBOPLATIN** (Paraplatin®) NSC #241240 (092006)

Source and Pharmacology: The mechanism of action of carboplatin would appear to be similar to that of cisplatin. It binds to replicating DNA causing single strand breaks and interstrand cross-links with DNA. Data suggests that other factors also contribute to cytotoxicity. The α $t_{½}$ is 1.1 to 2 hours and the β $t_{½}$ is 2.6 to 5.9 hours. Carboplatin is not protein bound. The major route of elimination of carboplatin is renal excretion. Patients with creatinine clearances of approximately 60 mL/min or greater excrete 65% of the dose in the urine within 12 hours and 71% of the dose within 24 hours. In patients with creatinine clearances below 60 mL/min the total body and renal clearances of carboplatin decrease as the creatinine clearance decreases. Carboplatin dosages will require adjustment dependent on the glomerular filtration rate.

Toxicity:

	Common Happens to 21-100 out of every 100 children	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting	Hypersensitivity reactions[2] (anaphylaxis, bronchospasm, hypotension), constipation, diarrhea	Metallic taste, rash, mucositis
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression[1] (anemia, neutropenia, leukopenia, thrombocytopenia), Electrolyte abnormalities (↓ Na, K, Ca, Mg)	↑ LFT's (Alk Phos, AST), abdominal pain, nephrotoxicity (↓ GFR, ↑ Cr and BUN), asthenia	↑ bilirubin
Delayed: Any time later during therapy		ototoxicity (tinnitus, hearing loss)	Peripheral neuropathy with mild paresthesias, diminished sense of vibration, light touch, pinprick, and joint position, alopecia; temporary loss of vision to light and colors
Late: Any time after completion of treatment			Secondary leukemia
Unknown Frequency and Timing	Fetal toxicities and teratogenic effects of carboplatin have been noted in animals and may cause fetal harm when administered to pregnant women. It is unknown whether the drug is excreted in breast milk.		

[1] *Thrombocytopenia is more severe or dose limiting.*
[2] *Hypersensitivity reactions are seen more frequently with repeated courses of therapy (after six courses in adults).*
(L) Toxicity may also occur later.

Formulation and Stability:
Carboplatin is available in 50mg, 150mg and 450 mg vials and 600mg vials.
Aqueous Solution:
Carboplatin aqueous solution is supplied as a sterile, pyrogen-free, 10 mg/mL aqueous solution of carboplatin in multidose vials.
Unopened vials of carboplatin aqueous solution are stable to the date indicated on the package when stored at 25° C (77° F); excursions permitted from 15°-30° C (59°-86° F). Protect from light. Carboplatin aqueous solution multidose vials maintain microbial, chemical, and physical stability for up to 14 days at 25° C following multiple needle entries.

Powder for Injection:
Carboplatin powder for injection is a sterile lyophilized white powder in single dose vials containing equal parts by weight of carboplatin and mannitol. Unopened vials of carboplatin are stable to the date indicated on the package when stored at 15°-30° C (59°-86° F). Protect from light.

Guidelines for Administration: See Treatment and Dose Modifications sections of the protocol.

I.V.: Reconstitute lyophilized powder to concentration of 10 mg/ml with sterile water for injection, 5% Dextrose, Normal Saline or use premixed 10mg/ml aqueous solution. May further dilute in dextrose or saline containing solutions to a final concentration as low as 0.5mg/ml and infuse over 60 minutes. Carboplatin solutions, when prepared as directed are stable for 8 hours at room temperature.

Aluminum can react with carboplatin, causing precipitate formation and potency loss. Do not use needles or IV administration sets containing aluminum parts that may come in contact with carboplatin for the preparation or administration of the drug.

Supplier: Commercially available from various manufacturers. See package insert for more detailed information.

7.2 **CYCLOPHOSPHAMIDE** (Cytoxan) NSC #26271 (082006)

Source and Pharmacology: Cyclophosphamide is an alkylating agent related to nitrogen mustard. Cyclophosphamide is inactive until it is metabolized by P-450 isoenzymes (CYP2B6, CYP2C9 and CYP3A4) in the liver to active compounds. The initial product is 4-hydroxycyclophosphamide (4-HC) which is in equilibrium with aldophosphamide which spontaneously releases acrolein to produce phosphoramide mustard. Phosphoramide mustard, which is an active bifunctional alkylating species, is 10 times more potent in vitro than is 4-HC and has been shown to produce interstrand DNA cross-link analogous to those produced by mechlorethamine. Approximately 70% of a dose of cyclophosphamide is excreted in the urine as the inactive carboxyphosphamide and 5-25% as unchanged drug.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Anorexia, nausea & vomiting (acute and delayed)	abdominal discomfort, Diarrhea	Transient blurred vision, nasal stuffiness with rapid administration, arrhythmias (rapid infusion), skin rash, anaphylaxis, SIADH
Prompt: Within 2-3 weeks, prior to the next course	Leukopenia, alopecia, Immune suppression	Thrombocytopenia, Anemia, Hemorrhagic cystitis (L),	Cardiac toxicity with high dose (acute – CHF hemorrhagic myocarditis, myocardial necrosis) (L), hyperpigmentation, nail changes, impaired wound healing, Infection secondary to immune suppression
Delayed: Any time later during therapy, excluding the above conditions	Gonadal dysfunction : azoospermia or oligospermia (prolonged or permanent)[1] (L)	amenorrhea[1]	gonadal dysfunction : ovarian failure[1] (L) Interstitial pneumonitis, pulmonary fibrosis[2](L),
Late: Any time after completion of treatment			Secondary malignancy (ALL, ANLL, AML), bladder carcinoma (long term use > 2 years), bladder fibrosis
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of cyclophosphamide (alone or in combination with other antineoplastic agents) have been noted in humans. Toxicities include: chromosomal abnormalities, multiple anomalies, pancytopenia, and low birth weight. Cyclophosphamide is excreted into breast milk. Cyclophosphamide is contraindicated during breast feeding because of reported cases of neutropenia in breast fed infants and the potential for serious adverse effects.		

[1] *Dependent on dose, age, gender and degree of pubertal development at time of treatment*
[2] *Risk increased with chest radiation and high dose.*
(L) Toxicity may also occur later.

Formulation and Stability:
Cyclophosphamide for Injection is available as powder for injection or lyophilized powder for injection in 500 mg, 1 gm and 2 gm vials. The powder for injection contains 82 mg sodium bicarbonate/100 mg cyclophosphamide and the lyophilized powder for injection contains 75 mg mannitol/100 mg cyclophosphamide. Storage at or below 25ºC (77ºF) is recommended. The product will withstand brief exposures to temperatures up to 30º C (86ºF).

Guidelines for Administration: See Treatment and Dose Modifications sections of the protocol.

Cyclophosphamide for Injection: Reconstitute with sterile water or Bacteriostatic water for injection (paraben preserved only) to a concentration of 20 mg/ml. Solutions reconstituted with preservative should be used within 24 hours if stored at room temperature or within 6 days if stored under refrigeration. If administered as undiluted drug at the 20 mg/ml concentration, reconstitute with NS only to avoid a hypotonic solution.

Cyclophosphamide may be further diluted in dextrose or saline containing solutions for IV use.

Supplier: Commercially available from various manufacturers. See package insert for further information

7.3 **ETOPOSIDE** (VePesid®, Etopophos®,VP-16) NSC #141540 (112005)

Source and Pharmacology: A semisynthetic derivative of podophyllotoxin that forms a complex with topoisomerase II and DNA which results in single and double strand DNA breaks. Its main effect appears to be in the S and G_2 phase of the cell cycle. The initial t½ is 1.5 hours and the mean terminal half-life is 4 to 11 hours. It is primarily excreted in the urine. In children, approximately 55% of the dose is excreted in the urine as etoposide in 24 hours. The mean renal clearance of etoposide is 7 to 10 mL/min/m² or about 35% of the total body clearance over a dose range of 80 to 600 mg/m². Etoposide, therefore, is cleared by both renal and non renal processes, i.e., metabolism and biliary excretion. The effect of renal disease on plasma etoposide clearance is not known. Biliary excretion appears to be a minor route of etoposide elimination. Only 6% or less of an intravenous dose is recovered in the bile as etoposide. Metabolism accounts for most of the non renal clearance of etoposide.

The maximum plasma concentration and area under the concentration time curve (AUC) exhibit a high degree of patient variability. Etoposide is highly bound to plasma proteins (~94%), primarily serum albumin. Pharmacodynamic studies have shown that etoposide systemic exposure is related to toxicity. Preliminary data suggests that systemic exposure for unbound etoposide correlates better than total (bound and unbound) etoposide. There is poor diffusion into the CSF < 5%.
Cmax and AUC values for orally administered etoposide capsules consistently fall in the same range as the Cmax and AUC values for an intravenous dose of one-half the size of the oral dose. The overall mean value of oral capsule bioavailability is approximately 50% (range 25-75%).
Etoposide phosphate is a water soluble ester of etoposide which is rapidly and completely converted to etoposide in plasma. Pharmacokinetic and pharmacodynamic data indicate that etoposide phosphate is bioequivalent to etoposide when it is administered in molar equivalent doses.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting	Anorexia	Transient hypotension during infusion; anaphylaxis (chills, fever, tachycardia, dyspnea, bronchospasm, hypotension)
Prompt: Within 2-3 weeks, prior to next course	Myelosuppression (anemia, leukopenia), alopecia	thrombocytopenia, diarrhea, abdominal pain, asthenia, malaise, rashes and urticaria	Peripheral neuropathy, mucositis, hepatotoxicity, chest pain, thrombophlebitis, congestive heart failure, Stevens-Johnson Syndrome, exfoliative dermatitis
Delayed: Any time later during therapy			Dystonia, ovarian failure, amenorrhea, anovulatory cycles, hypomenorrhea, onycholysis of nails
Late: Any time after completion of treatment			Secondary malignancy (preleukemic or leukemic syndromes)
Unknown Frequency and Timing: Fetal toxicities and teratogenic effects of etoposide have been noted in animals at 1/20th of the human dose. It is unknown whether the drug is excreted in breast milk.			

Formulation and Stability:

Etoposide for Injection is available in sterile multiple dose vials. The pH of the clear, nearly colorless to yellow liquid is 3 to 4. Each mL contains 20 mg etoposide, 2 mg citric acid, 30mg benzyl alcohol, 80 mg modified polysorbate 80/tween 80, 650 mg polyethylene glycol 300, and 30.5 percent (v/v) alcohol. Vial headspace contains nitrogen.

Unopened vials of Etoposide are stable until expiration date on package at room temperature (25°C).

Etoposide phosphate for injection is available for intravenous infusion as a sterile lyophilized powder in single-dose vials containing etoposide phosphate equivalent to 100 mg etoposide, 32.7 mg sodium citrate USP, and 300 mg dextran 40.

Etoposide phosphate must be stored under refrigeration 2°-8°C (36°- 46°F). Unopened vials of etoposide phosphate are stable until the expiration date on the package.

Etoposide capsules must be stored under refrigeration 2°-8°C (36°- 46°F). The capsules are stable until the expiration date on the package.

Guidelines for Administration: See Treatment and Dose Modification sections of the protocol.

Etoposide:
Dilute Etoposide to a final concentration ≤0.4 mg/mL in Dextrose or Normal Saline containing IV solutions.
Etoposide infusions are stable at room temperature for 96 hours when diluted to concentrations of 0.2mg/ml; stability is 24 hours at room temperature with concentrations of 0.4mg/mL. The time to precipitation is highly unpredictable at concentrations > 0.4mg/mL. Administer over 30 to 60 minutes. **Do not administer etoposide by rapid intravenous injection.**
To avoid leaching of DEHP from PVC bags and tubing, prepare the Etoposide solution as close as possible preferably within 4 hours to the time of administration or alternatively as per institutional policy, non-PVC containers and tubing may be used.

Etoposide Phosphate:
Dilute the 100 mg vial with 5 or l0 mL of Sterile Water for Injection, USP; 5% Dextrose Injection, USP; 0.9% Sodium Chloride Injection, USP; Bacteriostatic Water for Injection with Benzyl Alcohol; or Bacteriostatic Sodium Chloride for Injection with Benzyl Alcohol for a concentration equivalent to 20 mg/mL or 10 mg/mL etoposide (22.7 mg/mL or 11.4 mg/mL etoposide phosphate) respectively.

When reconstituted with diluent containing a bacteriostat, etoposide phosphate solutions can be stored in glass or plastic containers under refrigeration at 2˚-8˚C (36˚-46˚F) for 7 days or at controlled room temperature 20˚-25˚C (68˚-77˚F) for 48 hours; following reconstitution with Sterile Water for Injection, USP, 5% Dextrose Injection, USP, or 0.9% Sodium Chloride USP store at controlled room temperature 20˚-25˚C (68˚-77˚F) for 24 hours.
Following reconstitution, etoposide phosphate may be further diluted to concentrations as low as 0.1 mg/mL etoposide with Dextrose or Saline infusion solutions. Etoposide Phosphate may be administered as a bolus or by IV infusion at rates from 5 to 210 minutes.

Supplier: Commercially available from various manufactures. See package insert for more detailed information.

7.4 Filgrastim, (Granulocyte Colony-Stimulating Factor, r-metHuG-CSF, G-CSF, Neupogen®) NSC #614629 (032007)

Source and Pharmacology: Filgrastim is a human granulocyte colony-stimulating factor (G-CSF), produced by recombinant DNA technology. Filgrastim is a 175 amino acid protein with a molecular weight of 18,800 daltons manufactured by recombinant DNA technology utilizing E coli bacteria into which has been inserted the human granulocyte colony stimulating factor gene. It differs from the natural protein in that the N- amino acid is methionine and the protein is not glycosylated. G-CSF is a lineage specific colony-stimulating factor which regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens). The elimination half-life is similar for subcutaneous and intravenous administration, approximately 3.5 hours. The time to peak concentration when administered subcutaneously is 2 to 8 hours

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Local irritation at the injection site, headache	Allergic reactions (more common with IV administration than subcutaneous):skin (rash, urticaria, facial edema), respiratory (wheezing, dyspnea) and cardiovascular (hypotension, tachycardia), low grade fever
Prompt: Within 2-3 weeks, prior to the next course	Mild to moderate medullary bone pain,	Increased: alkaline phosphatase, lactate dehydrogenase and uric acid, thrombocytopenia	Splenomegaly, splenic rupture, exacerbation of pre-existing skin rashes, sickle cell crises in patients with SCD, excessive leukocytosis
Delayed: Anytime later during therapy			Cutaneous vasculitis, ARDS
Late: Anytime after completion of treatment			MDS or AML (confined to patients with severe chronic neutropenia and long term administration)
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of filgrastim in humans are unknown. Conflicting data exist in animal studies and filgrastim is known to pass the placental barrier. It is unknown whether the drug is excreted in breast milk.		

Formulation and Stability: Supplied as a clear solution in 300 mcg/ml 1 ml or 1.6 ml vials and prefilled syringes containing 300mcg/0.5mL or 480mcg/0.8mL. Vials are preservative free single use vials. Discard unused portions of open vials. Store refrigerated at 2-8º C (36-46ºF). Prior to injection, filgrastim may be allowed to reach room temperature for a maximum of 24 hours. Avoid freezing and temperatures > 30ºC.

For IV use, dilute in D5W **only** to concentrations >15 mcg/ml. At concentrations between 5 and 15 mcg/ml, human serum albumin should be added to make a final albumin concentration of 0.2% (2 mg/ml) in order to minimize the adsorption of filgrastim to infusion containers and equipment. Dilutions of 5mcg/ml or less are not recommended. Diluted filgrastim should be stored at 2-8º C (36-46ºF) and used within 24 hours. **Do not shake.**

Guidelines for Administration:
Filgrastim should not be administered within 24 hours of chemotherapy.

Supplier: Commercially available from various manufacturers. See package insert for further information

7.5 **MESNA** (sodium 2-mercaptoethane sulfonate,UCB 3983, Mesnex®) NSC #113891 (092006)

Source and Pharmacology: Mesna was developed as a prophylactic agent to reduce the risk of hemorrhagic cystitis induced by ifosfamide. Mesna is rapidly oxidized to its major metabolite, mesna disulfide (dimesna). Mesna disulfide remains in the intravascular compartment and is rapidly eliminated by the kidneys. In the kidney, the mesna disulfide is reduced to the free thiol compound, mesna, which reacts chemically with the urotoxic ifosfamide metabolites (acrolein and 4-hydroxy-ifosfamide) resulting in their detoxification. The first step in the detoxification process is the binding of mesna to 4-hydroxy-ifosfamide forming a nonurotoxic 4-sulfoethylthioifosfamide. Mesna also binds to the double bonds of acrolein and to other urotoxic metabolites. In multiple human xenograft or rodent tumor model studies, mesna in combination with ifosfamide (at dose ratios of up to 20-fold as single or multiple courses) failed to demonstrate interference with antitumor efficacy.

After an 800mg dose the half lives for Mesna and DiMesna are 0.36 hours and 1.17 hours, respectively. Approximately 32% and 33% of the administered dose was eliminated in the urine in 24 hours as mesna and dimesna, respectively. The majority of the dose recovered was eliminated within 4 hours. Mesna tablets have an oral bioavailability of 45-79% and a urinary bioavailability which ranged from 45-79% of intravenously administered mesna. The oral bioavailability is unaffected by food. When compared to intravenously administered mesna, the intravenous plus oral dosing regimen increases systemic exposures (150%) and provides more sustained excretion of mesna in the urine over a 24-hour period.

Toxicity[1]:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to <5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Bad taste with oral use	Nausea, vomiting, Stomach pain, fatigue, Headache,	Facial flushing, fever, pain in arms, legs, and joints, rash, Transient hypotension, Tachycardia, dizziness, anxiety, Confusion, periorbital swelling, Anaphylaxis, coughing
Prompt: Within 2-3 weeks, prior to the next course		Diarrhea	
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of mesna have not been noted in animals fed 10 times the recommended human doses. There are however no adequate and well-controlled studies in pregnant women. It is not known if mesna or dimesna is excreted into human milk		

[1]*All currently available products in the U.S. are preserved with benzyl alcohol. Benzyl Alcohol has been associated with death in pre-term infants weighing less than 2500 gms and receiving 99-405 mg/kg/day. Benzyl alcohol is normally oxidized rapidly to benzoic acid, conjugated with glycine in the liver, and excreted as hippuric acid .In pre-term infants, however, this metabolic pathway may not be well developed. Onset of toxic illness in these infants occurred between several days and a few weeks of age with a characteristic clinical picture that included metabolic acidosis progressing to respiratory distress and gasping respirations. Many infants also had central-nervous-system dysfunction, including convulsions and intracranial hemorrhage; hypotension leading to cardiovascular collapse was a late finding usually preceding death. [For comparison in the ICE regimen of 3000mg/m²/day of ifosfamide and a daily mesna dose of 60% of the ifosfamide dose = to 1800mg/m²/day; a child would be expected to*

receive 18 ml/m²/day of mesna (concentration of 100mg/ml and 10.4mg/ml of benzyl alcohol) 187.2 mg/m²/day of benzyl alcohol or 6.24mg/kg/day.]

Formulation and Stability: Available as 400mg oral tablets. Excipients include lactose, microcrystalline cellulose, calcium phosphate, cornstarch, povidone, magnesium stearate, hydroxypropylmethylcellulose, polyethylene glycol, titanium dioxide, and simethicone.

Mesna for injection is available as 100mg/ml 10ml multidose vials which contain 0.25 mg/mL edetate disodium and sodium hydroxide for pH adjustment. Mesna Injection multidose vials also contain 10.4 mg/ml of benzyl alcohol as a preservative. Store product at controlled room temperature 15-25°C (68-77ºF). Mesna is not light-sensitive, but is oxidized to DiMesna when exposed to oxygen. Mesna as benzyl alcohol-preserved vials may be stored and used for 8 days.
Mesna non-preserved ampoules are no longer provided by Bristol-Myer Squibb Company.

Guidelines for Administration: See Treatment Dose Modifications and Supportive Care sections of the protocol.

For IV administration, dilute to 20 mg/mL with dextrose or saline containing solutions. Mesna may be mixed with ifosfamide or cyclophosphamide. After dilution for administration, mesna is physically and chemically stable for 24 hours at 25ºC (77ºF). Carefully expel air in syringes prepacked for use to avoid oxidation to dimesna.
Mesna may cause false positive test for urinary ketones.

Supplier: Commercially available from various manufacturers. See package insert for further information.

7.6 **VINCRISTINE SULFATE** (Oncovin®**,** VCR, LCR) NSC #67574 (72006)

Source and Pharmacology: Vincristine is an alkaloid isolated from Vinca rosea Linn (periwinkle). It binds to tubulin, disrupting mircotubules and inducing metaphase arrest. Its serum decay pattern is triphasic. The initial, middle, and terminal half-lives are 5 minutes, 2.3 hours, and 85 hours respectively; however, the range of the terminal half-life in humans is from 19 to 155 hours. The liver is the major excretory organ in humans and animals; about 80% of an injected dose of vincristine sulfate appears in the feces and 10% to 20% can be found in the urine. Within 15 to 30 minutes after injection, over 90% of the drug is distributed from the blood into tissue, where it remains tightly, but not irreversibly bound. It is excreted in the bile and feces. There is poor CSF penetration.

Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Jaw pain; headache	Extravasation (rare) but if occurs = local ulceration; shortness of breath and bronchospasm
Prompt: Within 2-3 weeks, prior to the next course	Alopecia, constipation,	Weakness, abdominal pain; , mild brief myelosupression (leucopenia, thrombocytopenia, anemia)	Paralytic ileus; ptosis, diplopia, night blindness; hoarseness; vocal cord paralysis; SIADH, seizure; defective sweating
Delayed: Any time later during therapy	Loss of deep tendon reflexes	Peripheral paresthesias including numbness, tingling and pain; clumsiness; wrist drop, foot drop; abnormal gait	Difficulty walking or inability to walk; veno-occlusive disease (in combination); blindness, optic atrophy; urinary tract disorders including bladder atony, dysuria, polyuria, nocturia, urinary retention; autonomic neuropathy with postural hypotension; 8th cranial nerve damage with dizziness, nystagmus, vertigo and hearing loss
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of vincristine (either alone or in combination with other antineoplastic agents) have been noted in humans. The toxicities include: chromosome abnormalities, malformation, pancytopenia, and low birth weight. It is unknown whether the drug is excreted in breast milk.		

Formulation and Stability:
Vincristine is supplied in a vial each mL of which contains vincristine sulfate, 1 mg (1.08 μmol); mannitol, 100 mg; sterile water for injection; Acetic acid and sodium acetate are added for pH control. The pH of Vincristine Sulfate Injection, USP ranges from 3.5 to 5.5. This product is a sterile solution. Store refrigerated at 2-8˚C or 36-46˚F. Protect from light and retain in carton until time of use.

Do not mix with any IV solutions other than those containing dextrose or saline.

Guidelines for Administration: See the Treatment and Dose Modifications Sections of protocol.

Injection of vincristine sulfate should be accomplished within 1 minute. Vincristine sulfate must be administered via an intact, free-flowing intravenous needle or catheter. Care should be taken to ensure that the needle or catheter is securely within the vein to avoid extravasation during administration. The solution may be injected either directly into a vein or into the tubing of a running intravenous infusion.

When dispensed the container or syringe containing vincristine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. Fatal if given intrathecally. For Intravenous use only."

Supplier: Commercially available from various manufacturers. See package insert for more detailed information.

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal From Protocol Therapy

a) Neuraxis dissemination (development of metastatic disease) during or after chemotherapy.

b) Neuraxis dissemination (development of metastatic disease) or locally progressive disease during or after radiation therapy.

c) Refusal of further protocol therapy by patient/parent/guardian.

d) Completion of protocol therapy.

e) Physician determines it is in patient's best interest.

Patients who have received protocol therapy are to be followed until they meet the criteria for off study (see below). Follow-up data will be required unless consent was withdrawn.

8.2 Off Study Criteria

a) Death

b) Lost to follow-up (this designation requires prior approval by the COG statistical office)

c) Entry into another C.O.G therapeutic study

d) Withdrawal of consent for any further data submission.

e) Tenth anniversary of study closure to accrual

9.0 NEUROSURGICAL GUIDELINES

9.1 General

When feasible, an attempt will be made to perform a gross total resection; if not feasible, an attempt will be made to remove as much tumor as possible without jeopardizing the patient. Biopsy alone, with no attempt at resection, may be associated with statistically worse survival and local progression during chemotherapy and should not be done. No patient will be eligible for this study without a pathologic diagnosis.

9.2 Imaging Confirmation of Extent of Resection

All patients will have confirmation of the neurosurgical staging of the extent of resection with a postoperative MRI with and without contrast. This scan should be carried out within 21 days after surgery, preferably within 72 hours. When the post-operative scan obtained within 72 hours is difficult to interpret, the scan should be repeated 10 or more days after surgery.

9.3 Peri-operative Corticosteroids

9.3.1
Some patients with large tumors may require initiation of corticosteroid therapy pre-operatively to reduce associated cerebral edema or improve neurologic function.

9.3.2
Usual corticosteroid dosage is 0.25 to 1 mg/kg/day of Dexamethasone, in divided doses, every 4-6 hours.

9.3.3
Corticosteroids may be continued during the peri-operative period. Every attempt should be made to taper and discontinue corticosteroid therapy as soon as clinically feasible (7 days).

9.4 Initial Surgery

9.4.1
The guidelines for surgery are provided with the recognition that many patients on this study will have had their first operation prior to referral to the oncology service. Control of significant hydrocephalus in the perioperative period may be achieved with placement of either a ventriculostomy or ventriculoperitoneal shunt at the discretion of the neurosurgeon. Patients are allowed to have had more than one attempt at resection prior to enrollment.

9.4.2
For infratentorial tumors, suboccipital craniotomy or craniectomy should be performed using standard neurosurgical procedures. Midline tumors are best approached by a midline incision extending to the upper cervical region. When appropriate, the posterior arch of C-1 should be removed as well so that the tonsils and brainstem can be decompressed. A wide dural opening will permit exposure of the cerebellar vermis, tonsils, medulla, both cerebellar hemispheres, and the upper cervical region. Careful search for extension of disease in the arachnoid and leptomeninges should be made. Biopsies of these sites should be performed if disease extension is suspected. Evidence of brainstem invasion should be sought and noted in the operative report if present. Replacement of overlying bone and posterior vertebral body elements should be reported. The use of Surgicel (Johnson & Johnson, Somerville, NJ) and other hemostatic products should be reported. The site of origin should be sought and described in the operative report.

9.4.3
Tumor should be removed and hemostasis achieved using standard techniques. The surgeon should try to remove as much of the tumor as is safely possible, without comprising function. If resection cannot be complete, surgeons should estimate in their reports the percentage of tumor removed.

9.4.4
As much tissue as possible should be submitted intact to the pathologists for their review. At the time of **diagnosis and at the second surgery** it is strongly encouraged that the specimens outlined in Section 13.0 of the protocol be sent to the Biopathology Center (BPC). Unsafe tumor resection should not be undertaken for the purposes of tissue banking; however, removed tumor tissue should not be discarded.

9.4.5
Techniques for bone and dura closure will be left to the discretion of the neurosurgeon. Post-operatively, patients should be monitored for hematoma formation and hydrocephalus. A decision concerning placement of a permanent VP shunt should be made within two weeks of tumor removal.

9.5 Second Operation

9.5.1
The definition of second surgery in this study is surgery performed after the administration of chemotherapy and prior to radiation therapy. The purpose of the second operation is to safely remove as much tumor, as possible that persists after induction chemotherapy. As outlined in the Background section of this protocol, complete resection of disease at diagnosis confers a survival advantage to patients. One objective of this study is to determine the feasibility of second operation after chemotherapy. The goal of this intervention is to confer the advantage of complete resection of disease to as many patients as possible. If it is determined pre-operatively that residual tumor cannot be removed in its entirety, serious consideration should be made to resect the tumor to a minimum level of disease. When second surgery is performed after chemotherapy, the patient will require conformal radiation therapy regardless of extent of resection or the presence or absence of tumor in the operative specimen. Second surgery should be performed within 30 days after completing chemotherapy (i.e., before day 52 of cycle B of chemotherapy). Conformal radiation therapy may then be given within 30 days after completing chemotherapy or second surgery. The timelines for the performance of second surgery and conformal radiation therapy are not rigid.

9.5.2
There is no limit to the number of surgery procedures performed prior to enrollment or following chemotherapy. We expect to see cases where "second" surgery is performed and post-operatively the institutional team determines that additional surgery is feasible or necessary prior to radiation therapy.

9.5.3
Guidelines for this operation are similar to those for the first operation; however, control of increased intracranial pressure and ventriculomegaly should not be concerns at this time. An approach most suitable to the child should be taken. The direction of approach can be either similar to the first operation or different from it depending on the site of residual disease and the judgement of the surgeon.

9.5.4
Surgery to resect residual tumor during the first year 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 local disease progression, which is highly unusual during the first year after radiation therapy. Advice should be sought from the study chair or surgical coordinators for this study. Viable residual tumor in the specimen does not constitute disease progression and the patient will be evaluated for disease control within the original stratum. 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.

9.6 **Extent of Resection Definition and Treatment**
See Section 4.1

10.0 NEURORADIOLOGY GUIDELINES

10.1 **Neuroimaging**
The neuroimaging (MR) examination is the basis for determining the extent of resection and subsequent therapy. The determination of residual disease is based on abnormal anatomy. Ependymoma has a mixed pattern of enhancement and requires evaluation with all available imaging sequences including enhanced and non-enhanced, T1 – weighted, T2 – weighted, proton density and Fluid Attenuated Inversion Recovery (FLAIR) techniques capable of water suppression to define residual tumor.

10.2 **MR Brain With and Without Contrast**
To document the degree of residual tumor, pre and post-operative MR imaging with and without contrast must be performed. Post-operative imaging of the brain should be done within 72 hours of surgery and prior to the onset of edema or gliosis which can make measurements of residual tumor difficult. If imaging cannot be obtained at this time, then it should be done within 21 days following surgery and preferably 10 days after surgery.

10.3 **Tumor Measurements**
The dimensions of the tumor will be recorded for the L-R, A-P and S-I dimensions. Measurements should include solid residual tumor or tumor cysts.

10.4 **Postoperative MR Spine With and Without Contrast**
An MRI with gadolinium of the entire spine is required **either** within 10 days prior to surgery or 10 or more days after surgery. The MRI of the spine should include the entire spine and must be performed in at least two planes. If there is significant motion artifact and/or hemorrhage, then the scan is not evaluable and should be repeated.

10.5 **Central Review**
Central review will be performed to confirm eligibility, response and relapse by the study neuroradiologists which means that submission of imaging is a requirement to receive credit for enrollment.

The following scans should be submitted for central review for all patients in addition to the operative report:

Head MR: Axial T1-weighted images without contrast; axial T1-weighted images with contrast; T2-weighted images; FLAIR images.
Spine MR: pre or post-operative sagittal T1 images with contrast at a minimum. Do not send T2 or proton density images.

The following scans and reports must be submitted:

	Scan	Brain	Spine
1)	Preoperative (initial)	X	X (pre or post-op)
2)	Postoperative	X	X (pre or post-op)
3)	Post Chemotherapy	X	X
4)	Post Second Surgery (When performed)	X	-
5)	Post RT (4 months following start of RT)*	X	-
6)	Relapse	X	X

* - This corresponds to the first required observation following protocol therapy.

The study committee requests submission of pre and post-operative imaging from any and all surgeries performed to resect tumor in addition to those noted above. This includes patients who have more that one surgery prior to enrollment or more than one surgery after chemotherapy.

10.6 **Address Information**

Copies of films of the required studies for central review should be forwarded to:

Quality Assurance Review Center
272 West Exchange St. Suite 101
Providence, RI 02903
Phone: (401) 454-4301
Fax: (401) 454-4683

Submission of Diagnostic Imaging data in digital format is preferred over hard copies of films. Digital files must be in Dicom format. These files can be burned to a CD and mailed to QARC. Multiple studies for the same patient may be submitted on one CD; however, please submit only one patient per CD. Institutions with PACS systems can contact QARC regarding installation of the COG Dicommunicator software that manages e-mailing studies securely to QARC. Contact Dicommunicator@QARC.org for further information.

11.0 RADIATION THERAPY GUIDELINES

Radiation Therapy for patients on COG protocols can only be delivered at approved COG RT facilities (See Administrative Policy 3.9, April 2004)

Submission of the radiation therapy treatment plan in digital format (either Dicom RT or RTOG format) is strongly encouraged. See the QARC website (www.QARC.org) for digital data submission information.

Conformal radiation therapy guidelines are similar to those used for other COG studies. Using ICRU-50 definitions[59] the gross tumor volume (GTV) will be the tumor bed and residual tumor, the clinical target volume (CTV) will be an anatomically defined margin of 1.0 cm surrounding the GTV and the planning target volume (PTV) will be a geometric margin of 0.3-0.5 cm to account for variation is daily treatment. All patients will receive 59.4 Gy using conventional fractionation (1.8 Gy per day) except patients less than 18 months of age with extent of resection defined as GTR1 or GTR2 who will receive 54 Gy (Table 11.3.4).

11.1 **Equipment**

11.1.1 Modality

X-rays with a nominal energy ≥ 4 MV. Proton beams may be used.

11.1.2 Calibration

The calibration of therapy machines used in this protocol shall be verified by the Radiological Physics Center.

11.1.3 Treatment Planning

Patients enrolled on this study must be treated using conformal radiation therapy treatment planning and delivery techniques. The term conformal radiation therapy is used to denote any of a spectrum of RT planning and delivery techniques that rely on 3-dimensional imaging to define target tumor and to distinguish it from normal tissue. For treatment to be conformal the following criteria must be met:

1) Three-dimensional imaging data (CT) are acquired with the patient in the treatment position.
2) Image data are used to delineate and reconstruct a gross target volume, clinical target volume, planning target volume, and specific normal or critical structures in 3-dimensions.
3) Radiation beams can be freely oriented in 3-dimensions for both the planning and delivery process, and structures traversed by the beam can be visualized with the eye of the beam.
4) The distribution of dose relative to the target volume or any structure is computable on a point by point basis in 3-dimensional space.
5) Institutions not equipped to perform conformal radiation therapy according to these guidelines should refer the patient to a participating COG institution with proven capabilities to comply with the outlined parameters.
6) Patients will be considered not evaluable if approved benchmarks are not on file at QARC. Centers participating in this protocol using 3D conformal techniques are required to complete the 3D Benchmark; those treating with IMRT must complete the IMRT Questionnaire and either the QARC Benchmark or irradiate the RPC's IMRT head and neck phantom. The Benchmark material can be obtained from the Quality Assurance Review Center (www.QARC.org) Contact the RPC (http://rpc.mdanderson.org/rpc) for information regarding their IMRT phantoms.

11.2 Target Volumes

11.2.1 3-D Target Volume Definitions

The volumes that will be targeted and treated are defined in this section. The definitions for the target volumes and treatment dosimetry will adhere as closely as possible to the ICRU Report-50[59] and Report 62[60] definitions whenever possible.

11.2.2 Gross Tumor Volume (GTV)

The GTV includes all gross residual tumor and/or the tumor bed at the primary site based on the initial pre-operative imaging examination that defines the tissues initially involved with disease anatomically and the post-operative and pre-irradiation neuroimaging examinations that identify residual disease and/or the tumor bed. The GTV in most cases will be a contracted or collapsed tumor bed.

11.2.3 Clinical Target Volume (CTV)

The 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 calvarium, 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 will be 1.0 cm for all patients.

11.2.4 Planning Target Volume (PTV)

A margin is added to the CTV in 3-dimensions to create the PTV. It is geometric and not anatomically defined. The purpose of the PTV is to account for uncertainty in immobilization, image registration and daily variability in patient positioning. For this study the PTV margin is 0.3-0.5 cm. Given that the CTV is confined to the intracranial space, the PTV may extend into or beyond bone but is unlikely to extend beyond the surface of the patient.

11.3 Dosimetry

11.3.1 Prescription Point

The prescription point for each target volume is at or near the center[1]. For the brain this may be a point other than the central axis.

If IMRT used, dose may be prescribed to an isodose surface that encompasses the PTV provided that the dose uniformity requirements in Section 11.3.6 are satisfied.

11.3.2 Dose Definition

Dose is to be specified in Gray (Gy)-to-muscle.

11.3.3 Prescribed Dose and Fractionation

The **total** dose is dependent upon the age of the patient and the presence of residual disease at the time of irradiation.

11.3.4 Total Dose

The total dose will be 59.4 Gy for all patients except those less than 18 months of age at the time of irradiation whose extent of resection is described as GTR 1 or GTR 2. These patients will receive 54.0 Gy. (See Table 11.3.4)

Table 11.3.4

Age at the Start of Radiation Therapy	Extent of Resection Prior to Radiation Therapy*	Total Dose
< 18 months	GTR1, GTR2	54.0 Gy
> 18 months	GTR1, GTR2	59.4 Gy
< 18 months	NTR, STR	59.4 Gy
> 18 months	NTR, STR	59.4 Gy

All fractionation is 1.8 Gy per day.
*GTR1, GTR2, NTR, STR: Extent of resection definitions see Section 4.1

11.3.5 Dose Fractionation

Patients will receive one fraction of 1.8 Gy per day, five days per week.

11.3.6 Dose Uniformity

No more than 10% of the PTV should receive more than 110% of the prescribed dose.

11.3.7 Prescription Volume

The goal is to prescribe to the highest isodose surface that encompasses both PTV and CTV with the least inhomogeneity. The entire PTV should be encompassed within the 100% isodose surface, although 95% is acceptable and no more than 10% of the PTV should receive greater than 110% of the prescription dose as evaluated by DVH. Without compromising the targeting rules, treatment should be planned to spare the spinal cord, brainstem, optic chiasm, and optic nerves from the highest doses resulting from dose

[1] This follows the recommendations in ICRU Report-50. Some institutions may have different practices. If this is the case, convert the figures given to your system. Do not use the uncorrected prescription dose if your prescription point is not "at or near the center of the target volume". For instance, if you prescribe to the certain isodose value adjust this (departmental) prescription point. Contact QARC if assistance is needed.

inhomogeneity. In the situation where the spinal cord or optic chiasm will exceed the specified tolerance levels, a reduction in the targeted volume (cone down), after the tolerance dose has been reached, will be required that may underdose the PTV, CTV or GTV in the region of the avoided critical structure (see Section 11.5).

11.3.8 Treatment Interruptions

Treatment will not be interrupted for anemia, leukopenia, or thrombocytopenia unless life threatening. Blood product support should be instituted according to institutional/protocol guidelines (Section 5.0). There is no minimum hemoglobin level during radiation therapy. For interruptions of more that 2 treatment days, please contact the Radiation Oncology Study Chair. The reason for any interruptions greater than 3 treatment days should be recorded in the patient's treatment chart and submitted with the QA documentation. There is no contingency to prescribe supplemental doses because of treatment interruptions.

11.4 Treatment Technique

11.4.1 Conformal Treatment:

Conformal (three-dimensional) planning is required for this study. Beam arrangements and treatment techniques should be used that minimize the dose to the auditory system (cochleae), hypothalamic-pituitary unit and supratentorial brain (*e.g., temporal lobes)* providing that they do not compromise treatment of the intended PTV.

11.4.2 Patient Position

The patient may be treated in the supine or prone position. Reproducible set-ups are critical therefore the use of immobilization devices and deep sedation or general anesthesia is strongly encouraged.

11.4.3 Field Shaping

Field-shaping is required. Shielding shall be at least 5 HVL thick. Multi-leaf collimation may be used.

11.4.4 Treatment Planning CT

A CT study with the patient in the treatment position is required for treatment planning. The CT section thickness should be less than or equal to 4 mm and include the region bounded by the thoracic inlet and the most cephalad aspect of the skull.

11.4.5 MR Registration

Registration of MR to CT is strongly encouraged for patients with ependymoma. Care should be taken that the MR and CT studies have similar spinal cord flexion/extension especially for those patients with posterior fossa tumors.

11.4.6 Timing of Imaging Studies

The treatment planning CT should be obtained as close as possible to the start of radiation therapy allowing for the time required for the planning process. Anytime within 2 weeks of the initiation of radiation therapy is suggested. MR imaging studies used adjunctively in the planning process may include the most recent post-operative imaging study for patients who proceed directly to radiation therapy, the most recent post-operative imaging study for patients who undergo second surgery or the study obtained at the completion of chemotherapy for the patients who are judged not to be candidates for second surgery. MR imaging studies to be registered to CT data obtained more than two weeks prior to the planning process may have limited value as the tumor bed may tend to shift soon after surgery.

11.5 **Organs at Risk (Normal Tissue Sparing)**

Table 11.5 Dose Constraints (maximum daily and total doses)

Spinal Cord	Fractions 1-30 1.85 Gy per fraction and total dose of 55.62 Gy Fractions 31-33 1.25 Gy per fraction and total dose of 7.50 Gy
Optic Chiasm	Fractions 1-30 1.85 Gy per fraction and total dose of 55.62 Gy Fractions 31-33 1.25 Gy per fraction and total dose of 7.50 Gy

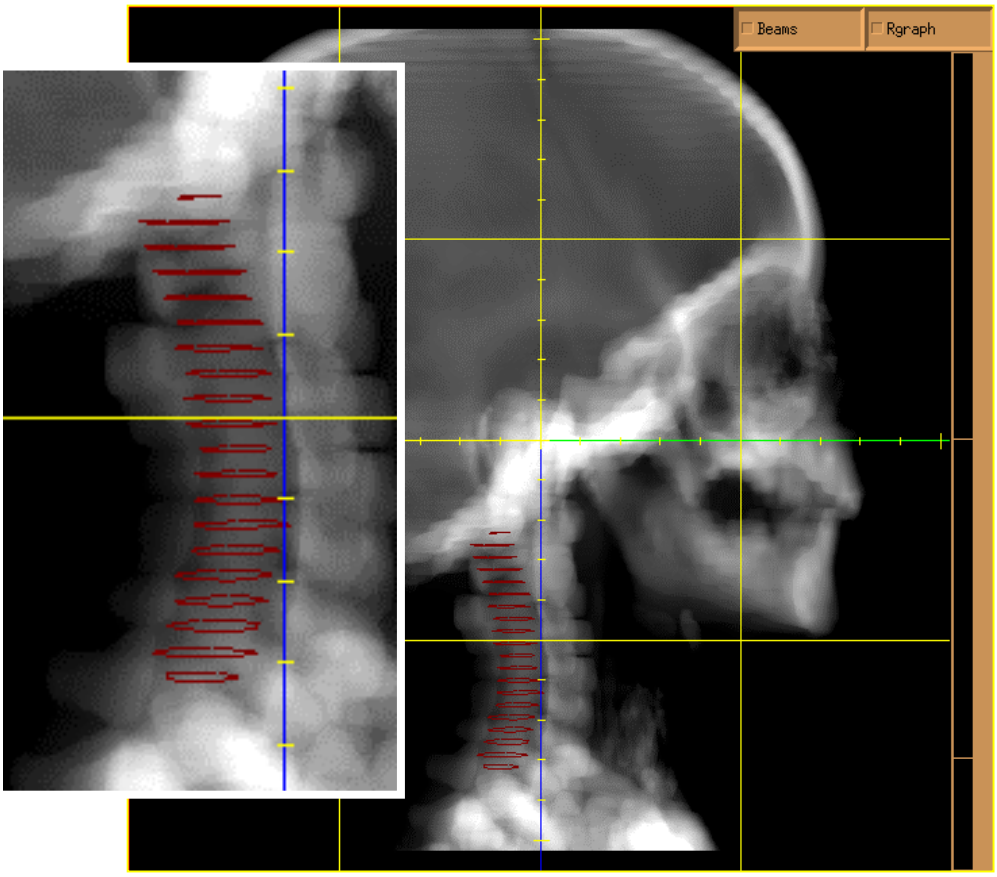
The specified normal tissue structures (spinal cord and optic chiasm) may receive additional dose above 54 Gy but only at a fraction of the daily dose (≤ 70% of 1.8 Gy or 1.25 Gy).

The best plan of action to observe spinal cord and optic chiasm tolerance is to treat the PTV to 54 Gy at 1.8 Gy per day during the first 30 fractions. Inhomogeneity of approximately 3% (1.85 Gy per fraction) is allowed but this volume should be minimized. For the final three fractions, the spinal cord and optic chiasm should be excluded so neither will receive more than 70% of the prescribed dose or 1.25 Gy per fraction.

11.5.1 Spinal Cord

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; 2.5 mm, n=24; 3 mm, n=20; 4 mm, n=15). The treatment should be planned without compromising the prescription guidelines, to minimize the dose to the spinal cord and to avoid inhomogeneity that would have the spinal cord receiving > 1.8 Gy per day. When the cumulative treatment dose has reached 54 Gy, the spinal cord should be excluded from the treatment and receive no more than 1.25 Gy per fraction at any point. These guidelines allow for underdosing of the targeted volumes after 54 Gy in selected cases. An example of the spinal cord defined for image section thickness of 3.0 mm is included in Figure 11.5.1.

Figure 11.5.1 Spinal cord defined on 20 successive CT images with section thickness 3 mm.



11.5.2 Optic Chiasm

The optic chiasm contour should appear on at least two successive MR or CT images. (See Table 11.5)

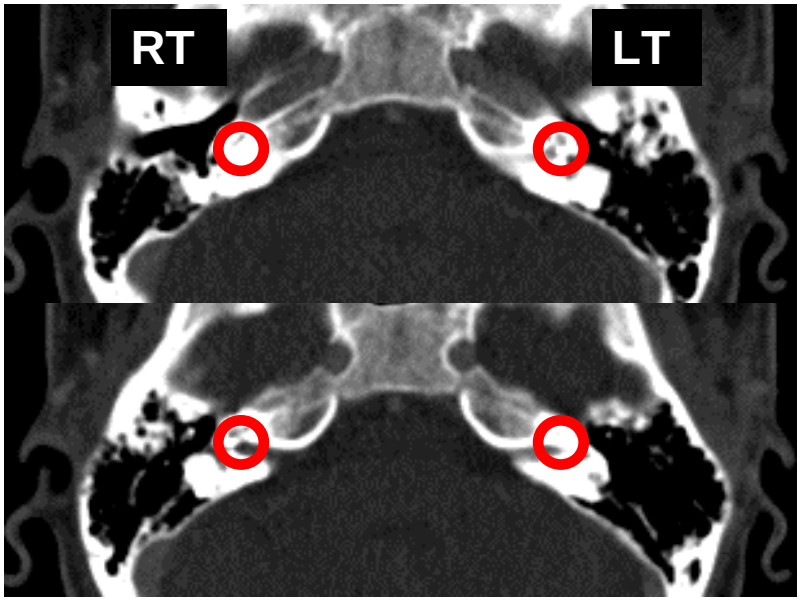
11.5.3 Cochlea

Each cochlea will be contoured on the CT data as a polygon or circular structure within the petrous portion of the temporal bone. The size and position of the contoured cochlea will be confirmed by viewing the structures in three dimensions using the treatment planning system. The contour should appear on at least two successive CT images (Figure 11.5.3).

11.5.4 Brainstem

There is no dose constraint for treatment of the brainstem on this protocol although infratentorial patients with a history of post-operative seizure(s), hypertension requiring medication and diffuse T2-weighted MR signal changes in the brainstem may require caution.

Figure 11.5.3 Right (RT) and left (LT) cochleae on CT images.



11.5.5
Fields should be specifically designed to minimize dose to critical structures such as the cochlea, hypothalamic-pituitary unit and supratentorial brain.

11.6 Dose Calculations and Reporting

11.6.1 Prescribed Dose

The monitor units required to deliver the prescribed dose to the prescription points for each of the planning target volumes shall be calculated and submitted using the "RT-3D Dosimetry Summary".

For IMRT techniques the monitor units required to deliver the prescribed dose shall be calculated and submitted using the IMRT Dosimetry Summary Form. The monitor units generated by the IMRT planning system must be independently checked prior to the patient's first treatment. Measurements in a QA phantom can suffice for a check as long as the plan's fluence distributions can be recomputed for a phantom geometry.

11.6.2 Dose Uniformity

The maximum and minimum dose for the PTV shall be calculated and reported on the "RT-3D Dosimetry Summary" form. These may be extracted from isodose diagrams, calculated separately or derived from the dose-volume histograms.

11.6.3 Isodose Distributions

Color hard copy isodose distributions for the total dose plan in the axial, sagittal, and coronal planes, which include the isocenter of the planning target volume (PTV), must be submitted. If sagittal and coronal planes are not available, then five axial distributions may be submitted (central axis, two superior and two inferior planes). These dose distributions must include a sufficient number of isodose contours to determine that the dose distribution conforms to the protocol guidelines. The isodoses should be superimposed over treatment planning CT or MR images. However, if such hard copy presents difficulty, similar plots without the gray scale are acceptable if enough critical contours are identifiable to verify the

dose distribution to target volumes and critical normal structures. Specifically, include those volumes for which there are dose volume histograms.

11.6.4 Dose Volume Histograms

Dose volume histogram will be calculated and submitted for normal tissues including the optic chiasm, pituitary, hypothalamus, total brain, temporal lobes (right and left), and spinal cord. Dose volume histograms will be calculated and submitted for the GTV, CTV and PTV. When a conedown is performed DVH data should be submitted for each volume, for each phase of treatment and as a composite.

11.7 Quality Assurance Documentation

If possible, the radiation therapy treatment plan should be submitted in digital format (either Dicom RT or RTOG format). See the QARC website (www.QARC.org) for digital data submission information. Data submitted in digital format should include the treatment planning CT, structure contours, treatment plans, 3D dose distributions, and DVH's. **All other radiotherapy data (i.e. RT-1 form or IMRT form, calculations, DRR's, BEV's, port films or portal images, patient photo with treatment fields marked) should be submitted in hard-copy format or as JPEG screen captures. We also request that you submit a hard copy isodose distribution in 3 orthogonal planes through the isocenter corresponding to the plan you submit digitally.**

11.7.1 Within three days of the start of radiotherapy, the following data shall be submitted for on-treatment review:

- Copies of the operative reports for each surgical procedure.
- Copies of the following diagnostic neuroimaging:
  - Pre-operative and post-operative cranial neuroimaging for each surgical procedure including second surgery after induction chemotherapy
  - Post chemotherapy (preRT) neuroimaging when no second surgery performed
- Copies of the treatment planning CT with the target volume (GTV, PTV) and normal tissue structures with dose constraints (e. g., spinal cord and optic chiasm) delineated
- First day portal films (or hard copy of real time portal images), simulator films (when available), and digitally reconstructed radiographs (DRR's) of each treatment portal.
- One set of orthogonal anterior/posterior and lateral films for isocenter localization for each group of concurrently treated beams. If portals being submitted contain an orthogonal set, this is sufficient.
- Pictures of the patient in the treatment position, with the fields marked on the skin or on the immobilization device and visible in the photograph (as feasible).
- RT-1 or IMRT Dosimetry Summary Form, whichever is applicable.
- Beam's Eye View (BEV's) of portals showing collimator, beam aperture, target volume and critical structures.*
- A Room's Eye View (REV), i.e., a composite illustration of all the fields and their angles, if available from your planning system.* Otherwise submit an overview diagram or illustration of the patient with all beams and their orientation indicated.
- Copies of the isodose distributions as required in 11.6.3*
- Dose volume histograms (DVH's) as required by 11.6.4* If IMRT is used, a DVH shall also 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.
- Documentation of an independent check of the calculated dose if IMRT is used.

- Copies of worksheets and/or printouts used for calculations of monitor settings to give the prescribed dose

*Copies of documentation must be submitted in color. Black and white copies of color documentation are not acceptable.

For patients treated with 3D conformal therapy, an approved 3D benchmark must be on file at QARC. If IMRT is used, the IMRT questionnaire and benchmark must be completed and approved before the patient can be evaluated. Contact QARC for any questions.

11.7.2 Within one week of the completion of radiotherapy, the following data shall be submitted.

- A copy of the patient's radiotherapy record including the prescription, and daily and cumulative doses to all required areas
- RT-2 Total Dose Summary Form
- Copies of additional DRR's and verification (portal) films for any field modifications made subsequent to the initial reporting of data for on-treatment review.
- An RT-1 dosimetry summary form, if changes have been made subsequent to submission of the on-treatment review data
- Copies of isodose distributions and calculations performed subsequent to the submission of the on-treatment data
- Dose volume histograms (DVH's) for the target volume and normal tissue structures, if modifications have been made subsequent to the DVH's submitted on-treatment

11.7.3 Address

The data should be sent to:

Quality Assurance Review Center
272 West Exchange St. Suite 101
Providence, RI 02903
Phone: (401) 454-4301
Fax: (401) 454-4683

11.7.4 Questions

Questions regarding the dose calculations or documentation should be directed to:

Protocol Dosimetrist
Quality Assurance Review Center
272 West Exchange St. Suite 101
Providence, RI 02903
Phone: (401) 454-4301
Fax: (401) 454-4683

Questions regarding the radiotherapy section of this protocol should be directed to:

Thomas E. Merchant, D.O., Ph.D.
Division of Radiation Oncology
St. Jude Children's Research Hospital
Memphis, Tennessee 35105
Telephone: (901) 495-3604
Telephone after 5PM Central (901) 495-3300
Fax: (901) 495-3113
E-mail: thomas.merchant@stjude.org

If unavailable, contact:

Eric L. Chang, MD
Department of Radiation Oncology
MD Anderson Cancer Center
1515 Holcombe Boulevard Box 97
Houston, Texas 77037
Telephone: (713) 792-3400
Fax: (713) 794-5573
E-mail: echang@mdanderson.org

11.8 Definitions of Deviation in Protocol Performance

11.8.1 Prescription

For volume-based treatment plans, the following definitions apply:

11.8.1.1 Minor Deviation

The delivered dose to the prescription point differs from protocol specification by more than 5% but less than 10%. Also, a minor deviation is scored if the 95% isodose surface covers <90% of the PTV or less than 100% but more than 90% of the CTV. Allowances will be made at the level of the spinal cord and chiasm in order to comply with tolerance guidelines – for conedowns only.

11.8.1.2 Major Deviation

The delivered dose to the prescription point differs from protocol specification by more than 10%. Also, a major deviation is scored if the 95% isodose surface covers less than 90% of the CTV, or if normal tissue sparing for the spinal cord is exceeded. Allowances will be made at the level of the spinal cord and chiasm in order to comply with tolerance guidelines – for conedowns only.

11.8.2 Dose Uniformity

11.8.2.1 Minor Deviation

More than 10% but less than 20% of the PTV receives more than 110% of the prescription dose.

11.8.2.2 Major Deviation

More than 20% of the PTV receives more than 110% of the prescription dose.

11.8.3 Volume

11.8.3.1 Minor Deviation

Margins for CTV or PTV less than specified, or field(s) excessively large.

11.8.3.2 Major Deviation

Transecting GTV.

12.0 NEUROPSYCHOLOGIC STUDIES

Note: Institutions are encouraged to enroll patients on the new ALTE07C1 protocol as soon as it is available.

Because of the high risk of neurodevelopmental problems in young children treated for ependymoma, assessment of functional and neuropsychological status will be completed to obtain information about tumor and treatment related morbidity. The premise of this study is that newer radiation planning and delivery techniques are capable of reducing neuropsychological sequela for all children, including the very young. While it has historically been difficult to obtain neuropsychometric data in a cooperative group study, these data are nonetheless critical to the success of this treatment approach and its acceptance by patients, parents and the neurooncology community.

After correcting for other factors responsible for neurocognitive function in children with CNS tumors, evidence exists to suggest that total dose and volume of irradiation play a major role in altering the neuropsychological status or intellectual outcome. A prime example of dose and volume effect is seen in the data of Hoppe-Hirsch et al.[58] who showed that the intellectual outcome in children with malignant tumors of the posterior fossa is influenced by the field of irradiation and the quality of surgery. Evaluated 1-2 years after surgery, 70-80 % of children maintained an IQ > 90 when no operative complications occurred, compared to 20-40 % following postoperative complications. Relative to radiation volume, 90 percent of children with ependymoma (treated to the posterior fossa alone) maintained an IQ > 90 at 5-10 years. This compares to the IQ performance of children with medulloblastoma (treated with full dose craniospinal irradiation to 25-35 Gy and a boost to the posterior fossa) in whom 20 percent at five years and 10 percent at 10 years maintained an IQ > 90.

In a meta-analysis, Mulhern and others[59] compared children treated to the neuraxis to those treated with focal irradiation. They found that those who received cranial irradiation had significantly lower IQ values than those who did not receive irradiation. There was no difference in IQ values between those treated with focal irradiation compared to those who received no irradiation. Because of multiple concurrent sources of potential neuropsychological dysfunction, all patients should be prospectively and serially evaluated using standardized methods of assessment.

12.1 **Objectives**

12.1.1
Document the percentage of children whose broad cognitive functioning remains at or above baseline functioning (baseline measure +/- 0.5 SD) up to four years after beginning radiation therapy.

12.1.2
Document the percentage of children whose neuropsychological functioning in specific domains remains intact (baseline measure +/- 0.5 SD) up to four years after beginning radiation therapy.

12.1.3
Determine the relationship between the temporal lobe dose distribution and both broad and specific longitudinal neurocognitive functioning.

12.1.4
Determine the influence of clinical and treatment variables on subsequent achievement/performance.

12.1.5
Determine the influence of clinical and treatment variables on health-related quality of life.

12.2 **Evaluations**
Testing will be required at three time points: Within one month of beginning RT; 24 (+/- 2) months after beginning RT; and 48 (+/- 2) months after beginning RT. Age-appropriate tests will be used and will include measures of broad cognitive functioning (IQ), specific areas neuropsychological functioning, achievement/performance and quality of life. Total testing time should be 1-2 hours.

Please consider conducting annual evaluations to allow for consecutive evaluations using the same measurement tool.

12.3 **Tests and Outcome Measures**

12.3.1 Broad Cognitive Functioning
Bayley Scales of Infant Development – Second Edition (Mental and Motor Scales): The BSID-II is an individually administered, standardized test that will be given to assess mental and motor developmental functioning in infants. The MDI and PDI are to be computed. This measure will serve as an index of cognitive functioning in children 0-36 months.
Bayley, N. (1993). Bayley Scales of Infant Development: Second Edition. New York: The Psychological Corp.

Wechsler Preschool and Primary Scale of Intelligence – Revised (WPPSI-R): The WPPSI-R is an individually administered, standardized test that will be administered to assess intellectual functioning in preschool-age children (ages 36-72 months). All subtests are to be administered and Verbal, Performance and Full-Scale IQ scores are to be computed.

Wechsler, D. (1989). Wechsler Preschool and Primary Scale of Intelligence – Revised. New York: The Psychological Corp.

Wechsler Intelligence Scale for Children – Third Edition (WISC-III): The WISC-III is an individually administered, standardized test that will be used to assess verbal and nonverbal intellectual functioning in school-age (ages 72 months – 16 years) children. The WISC-III will be administered to children 6 years of age and above (to 15 yr. 11 mo.). All subtests should be administered and Verbal, Performance and Full-Scale IQ scores are to be computed.
Wechsler, D. (1991). Wechsler Intelligence Scale for Children – Third Edition. New York: The Psychological Corp.

Wechsler Adult Intelligence Scale – Third Edition (WAIS-III). The WAIS-III is an individually administered, standardized test that will be used to assess verbal and nonverbal intellectual functioning in older teens and young adults (ages 16 and above). All subtests should be administered and Verbal, Performance and Full-Scale IQ scores are to be computed.
Wechsler, D. (1997). Wechsler Adult Intelligence Scale – Third Edition. New York: The Psychological Corp.

12.3.2 Measures of Specific Neuropsychological Functioning (NEPSY)
The NEPSY is an individually administered battery of neuropsychological tests from which selected subtests can be administered to evaluate attention, executive function, language, visuospatial processing, sensorimotor functions, and memory in children 3-12 years of age. The NEPSY will be administered to all children diagnosed at age 8 years or younger, who will therefore complete all 3 evaluations prior to turning 13 years of age.
Korkman, M., Kirk, U. & Kemp, S. (1997). NEPSY. New York: The Psychological Corp.

Measurement of Achievement
Wechsler Individual Achievement Test – Second Edition (WIAT-II): The WIAT-II is an individually administered test providing information about an individual's level of achievement in a range of domains. The test will be administered to children ≥ 4 years of age.
Wechsler, D. (2001). Individual Achievement Test – Second Edition. New York: The Psychological Corp.

12.3.4 Measurement of Quality of Life
Pediatric Cancer Quality of Life Inventory-32 (PCQL-32): The PCQL-32 has been developed to be a standardized assessment instrument to assess systematically pediatric cancer patient's health-related quality of life outcomes. Recent studies of the PCQL-32 have shown it to have good psychometric properties, and to be easily administered and useful in this population. It will be administered directly to children diagnosed at ≥ 8 years of age, and to parents (on behalf of their children) for those patients 7 and under. Similar mode of assessment (i.e. child or parent) will be utilized throughout all 3 evaluations.

Varni, J.W., Katz, E.R., et al. (1998). The Pediatric Cancer Quality of Life Inventory (PCQL). I. Instrument development, descriptive statistics, and cross-informant variance. Journal of Behavioral Medicine, 21(2): 179-204.

13.0 NEUROPATHOLOGY GUIDELINES, CENTRAL PATHOLOGY REVIEW SPECIMEN REQUIREMENT AND BIOLOGY SPECIMEN REQUIREMENTS

13.1 Histological Grading

13.1.1 Differentiated Ependymoma – WHO II
Differentiated ependymoma (EP) will be the classic lesion with cellular tissue in which perivascular pseudorosettes are a requisite feature. Less cellular, more fibrillar regions may be present. Necrosis may be common. Unless very focal, and unaccompanied by regions of higher cellularity and mitotic activity, vascular endothelial proliferation is not permitted in this category.

13.1.2 Anaplastic Ependymoma (AEP) – WHO III
Anaplastic ependymoma will include only tumors with clearly defined ependymal differentiation, in the form of perivascular pseudorosettes. The defining features of "anaplasia" will be: 1) increased cellularity when compared to the cellular regions in EP, 2) cytological atypia, and 3) microvascular proliferation. The hypercellularity may be diffuse or focal and in the form of multiple rather well circumscribed regions that abutt those of lower cellularity. Atypia may be expressed as cells with increased nuclear/cytoplasmic ratios and coarse chromatin. Vascular proliferation, of the glomeruloid variety, should be found within or just outside of the hypercellular regions. The cellular anaplastic regions may be mitotically more active than those of lesser cellularity, although mitotic activity has not been quantified, nor has any threshold mitotic index been determined to directed the lesion into the AEP category. Grading may be difficult and because tumors have a spectrum of marked cellular tissue that is usually mitotically more active than less cellular components. For this reason, we require vascular proliferation for this category, except in the few cases where the aggressive-appearing histological qualities might be overt, and no vascular proliferation is present.

13.2 Central Pathology Review Required for All Patients

The classification and grading of the tumors will be performed according to the WHO criteria (*Louis D., Ohgaki H, Wiestler O, Cavenee W. -eds,, WHO Classification of Tumours of the Central Nervous System, IARC Press, Lyon, 2007*). A modification of these have been applied to a series of ependymoma with significant differences in outcome in patients with differentiated (WHO grade II) ependymoma and anaplastic (WHO grade III) ependymoma. The submission of the pathology material shall be made directly from the participating institutions. The pathology review committee may utilize unstained sections for KI-67. The remaining slides shall be kept as back up material, or shall be used to perform additional staining as needed. Pathological evaluation will be performed in a joint review format.

Required Materials for Central Pathology Review (Rapid or Standard Central Review):

1) 2 H&E stained slides from **ALL** available paraffin blocks
2) Representative paraffin embedded tissue block. If block is not available, submit 5 unstained slides from the most representative block. Please label block or slides with the institutional surgical pathology number and the patient's COG Patient ID Number.
3) Institutional pathology reports
4) Operative report(s)
5) Institutional Neuropathology Worksheet
6) COG Specimen Transmittal Form to accompany each shipment: Please use current form from https://memberschildrensoncologygroup.org/prot/generic.asp.

Please see below for information on whether to send a case for Rapid or Standard Central Review. Cases sent for Rapid Central Review must be marked for RAPID REVIEW and shipped Federal Express Priority Overnight using account number 2504-6481-9 within 5 days of enrollment. Cases for Standard Central Review are shipped by regular mail or using your institutions courier account within 5 days of enrollment to:

COG Biopathology Center
Columbus Children's Hospital
700 Children's Drive, WA1340
Columbus, OH 43205
Phone: (614) 722-2894
Fax: (614) 722-2897

Please label all pathology review materials with patient's COG Patient ID Number and the Surgical Path ID (SPID Number) from the corresponding pathology report.

13.2.1 Rapid Central Pathology Review

Only those patients with supratentorial primary tumor locations will require rapid central pathology review at study entry. Cases must be marked for rapid review and sent within 5 days of enrollment by Federal Express Priority Overnight to the Biopathology Center. If the case cannot be reviewed in a timely manner, (within 14 days of enrollment), notify the study chair.

Second Opinion for Discordant Diagnoses

In the event that the institutional pathology review returns a diagnosis of ependymoma but the rapid review returns a diagnosis other than ependymoma, the specimen will be returned to the COG Biopathology Center and sent to the second study reviewer for final confirmation. One week of additional time will be allotted.

Disposition of Patients Attempting Enrollment on the Observation Arm (Stratum 1)
Patients with supratentorial tumor location, extent of resection GTR1 and diagnosed with differentiated ependymoma are eligible for observation. In the event that the institutional pathology review returns a diagnosis of differentiated ependymoma but the rapid review returns a diagnosis of anaplastic ependymoma, the specimen will be returned to the COG Biopathology Center and sent to the second study reviewer for final confirmation. One week of additional time will be allotted. Patients with equivocal assessment of tumor grade will receive adjuvant therapy.

13.2.2 Standard Central Review of Pathological Data (Initial and Second Resection)
Within 5 days of enrollment, for patients with infratentorial primary tumor locations, submit materials for Standard Central Review. For all patients undergoing second surgery, submit materials for Standard Central Review within two weeks of second surgery.

13.3 **Equivocal Assessment of Tumor Grade**
Patients with equivocal assessment of tumor grade will receive radiation therapy (stratum 3 or 4). Patients with supratentorial tumor location and extent of surgery GTR1 who are classified as anaplastic ependymoma (WHO III) by institutional review and are later (retrospectively reviewed) found to have differentiated ependymoma (WHO II) will remain evaluable for analysis in their respective strata because post-operative radiation therapy is considered to be standard.

13.4 **Contingency to Rapid Central Pathology Review**
When institutional review determines that the tumor is ependymoma and the tumor cannot be reviewed in a timely manner (within 14 days of enrollment), including equivocal review of histologic grade, the patient will receive radiation therapy.

13.5 **Biology Specimen Requirements**
Process tumor specimens from first and second surgeries according to the guidelines included in the section on tissue procurement. Send snap frozen tissue and matched control blood specimens to the Biopathology Center in Columbus, Ohio. Portions of the tissue will be used for the molecular genetic studies, by Dr. Ching Lau and the remainder will be available for other approved biology studies of ependymoma.

13.5.1 Required Materials

At the time of **diagnosis and second surgery,** tumor tissue should be sent to the Biopathology Center for Biology Studies:

1) **Frozen Tumor Tissue**: As many 100 mg pieces of tissue as possible should be frozen in foil in liquid nitrogen within 10 minutes of removal. Frozen tissue should be sent on dry ice to the BPC. A minimum tumor tissue > 0.5 cm^2 is preferred.
   -If frozen tumor is not available, formalin-fixed block with >80% tumor should be sent although this will compromise the studies being performed. (Paraffin blocks will be retained at the BPC unless return is requested.)
   -If frozen tumor is not available **and** the institution cannot release blocks; three to ten 50 um scrolls should be sent and 10 unstained slides. (Please indicate percent tumor represented.)
2) **Peripheral Blood**: 5 cc of peripheral blood in a green top tube (sodium heparin) and 5 cc of blood in a purple top tube (EDTA) should be sent at room temperature any time before the initiation of therapy. Do not send if the patient has had a whole blood transfusion. For second surgeries, please send blood at this time also.
3) **COG Specimen Transmittal Form** to accompany each shipment. Please use current form available at http://memberschildrensoncologygroup.org/prot/generic.asp

Please label biology specimens with the patient's BPC Number, collection date and specimen type.

Institutions are encouraged to enroll and submit specimens for ACNS02B3. If enough material is available to meet the biology requirements of this protocol and still have enough material left to meet minimal banking requirement for ACNS02B3, then the institution could receive credit for both this therapeutic trial and ACNS02B3.

13.5.2 Specimen Shipment

All biology specimens obtained for this study can be shipped to the BPC in a Specimen Procurement Kit. This dual chambered kit allows for the shipment of room temperature and frozen specimens in the same container. Dry ice may be placed in either compartment of the kit, but should not be put in both. This kit contains most of the supplies necessary for shipping specimens to the BPC. Please call the BPC at 800-347-2486 in order to request specifically the ACNS0121 Specimen Procurement Kit.

Before placing the specimens in the Specimen Procurement Kit, package the individual specimen bags as follows:

1) Place the individual specimen bags into the watertight plastic biohazard diagnostic envelope with absorbent material and seal the envelope securely.

2) Place the biohazard diagnostic envelope into the pressure-proof Tyvek diagnostic envelope and seal securely.

3) Place the Tyvek diagnostic envelope into the shipping container compartment.

Follow the above procedure twice, once for the ambient specimens and once for the frozen specimens. Place the two types of specimens into separate shipping compartments, keeping the ambient and frozen specimens separated.

- Snap frozen tissue should be placed in one of the kit compartments with approximately 4 lbs. of dry ice. Layer ½ of the dry ice on the bottom of the compartment, add the specimens, fill with the remaining dry ice and place the styrofoam on top to secure specimens during shipment.
- Formalin-fixed specimens, slides and blood should be shipped in the other kit compartment at room temperature. Place the styrofoam insert on top of the kit compartment to secure specimens during shipment.
- Seal the kit securely with filament or other durable sealing tape. Complete the pre-printed Federal Express air-bill, insert it into the plastic pouch and attach the pouch to the top of the kit. Complete the dry ice label (UN 1845). Stick the dry ice, and Exempt Human Specimen labels to the side of the box.
- Specimen Kits should be shipped on Monday through Thursday for Tuesday through Friday delivery via Federal Express Priority Overnight using the BPC Federal Express Account number (1290-2562-0). If blood is collected on a Friday, it should be shipped by Priority Overnight for Saturday delivery. Please mark *For Saturday Delivery* on the air bill and contact the BPC before shipment.

Ship specimens to:

Biopathology Center
Columbus Children's Hospital
700 Children's Drive, WA1340
Columbus, OH 43205
Phone: (614) 722-2810
FAX: (614) 722-2897

14.0 STATISTICAL CONSIDERATIONS

The primary objective of the statistical analysis will be to estimate the 5-year event-free survival (EFS) of patients treated for ependymoma with the treatment strategy outlined in this protocol. Other objectives of the analysis will be to:

- Estimate the 5-year EFS in differentiated, supratentorial ependymoma for patients who undergo gross total resection (GTR1) and no subsequent treatment
- Estimate the rate of complete resection with second surgery after chemotherapy among patients with initial STR.
- Compare 5-years EFS between centrally reviewed differentiated ependymoma and anaplastic ependymoma
- Describe the pattern of failure in differentiated supratentorial ependymoma treated with surgery alone, and in other ependymoma patients treated with conformal radiation therapy.
- Analyze the association between the number and type of chromosome aberrations detected through comparative genomic hybridization (CGH), and treatment outcome and tumor histology.
- Describe the neuropsychological and quality of life outcome in this cohort of patients.

14.1 Patient Accrual

The yearly incidence of ependymoma in the U.S. population, projected from data from Surveillance, Epidemiology, and End-Results (SEER) registries from 1992 to 1997 shows 81 cases age < 5, 26 cases ages 5-9 years, 30 cases ages 10-14, 15 cases ages 15-19 and 18 cases ages 20-25. [63] Hence, approximately 170 cases of intracranial ependymoma should be diagnosed in the U.S. per year in 0 to 24 year olds, and thus approximately 100 cases per year in the 3 to 21 year age group. Experience from the most recent national study for average risk medulloblastoma, A9961, is relevant to the expected accrual on this study. U.S. yearly incidence of medulloblastoma is approximately 240 per year in the 3 to 20 year age category, with approximately 50% falling into the average risk category. COG institutions enrolled 120+ patients per year on study A9961. Although COG was not recruiting the entire U.S. incidence of this tumor, it is reasonable to assume that COG institutions can capture most of the yearly incidence of CNS tumors. Hence, a number equivalent to between 50% and 70% of the U.S. incidence of intracranial ependymoma, or 50 to 70 patients per year, will likely be enrolled on this study.

14.2 Study Duration

The planned study duration will be 5 years of accrual and a minimum of 2 additional years of follow-up after the last patient has been enrolled. This study will accrue for 5 years provided that total accrual of eligible and followed patients is projected to be between 250 and 350 patients. If annual accrual is slower than the required 50 patients per year, accrual will be extended until a minimum of 250 patients have been accrued, with final analysis two years after the end of accrual. If annual accrual is greater than 70 patients per year, the accrual will be terminated at 350 eligible and followed patients provided that subsequent follow-up is extended to provide projected average potential follow-up of at least 3 years at the time of final analysis.

These rules guarantee results at least as precise as those obtainable with the nominal 50 patients/year for 5 years with 2 years of follow-up. Hence the remaining discussion will relate to this nominal accrual rate and trial duration. The accrual rate of eligible and followed patients will be evaluated at month 12 of the study using the average accrual rate achieved between months 7 and 12, and again at month 18 of the study using the average accrual rate achieved between months 7 and 18. The latter estimate will be used to project the total accrual length of the study. Accrual rates of 35/year or less will be of concern.

14.3 **Sample Composition**

We assume that 33% of patients will be diagnosed with supratentorial lesions. Of these, 67% will be anaplastic histology, and 60% will have a gross total resection (GTR) or near total resection (GTR/NTR). Infratentorial lesions will be diagnosed in 67% of patients, of which 19% will be anaplastic histology and 40% will have a GTR/NTR. [37] Overall 2-year and 5-year event-free survival (EFS) is assumed to be approximately 70% and 50%, respectively, with treatment failures rare after 5 years. It is further assumed that anaplastic histology is associated with a 2-fold increased risk of failure compared to differentiated histology, and that GTR/NTR is associated with half of the risk of failure compared to <STR. The table below describes the predicted sample composition and outcome statistics based on these assumptions.

Location	Pathology	Resection Status	% Patients	Minimum Number of Patients (N=250)	2-Year EFS	5-Year EFS
Supratentorial	Anaplastic	GTR/NTR	13.3%	33	69%	49%
"	"	< STR	8.9%	22	48%	24%
"	Differentiated	GTR/NTR	6.7%	17	83%	70%
"	"	< STR	4.4%	11	69%	49%
Infratentorial	Anaplastic	GTR/NTR	5.0%	13	69%	49%
"	"	< STR	7.5%	19	48%	24%
"	Differentiated	GTR/NTR	21.7%	54	83%	70%
"	"	< STR	32.5%	81	69%	49%

14.4 Statistical Analysis of EFS

14.4.1 Study Endpoints For Analysis of Treatment Efficacy.

The primary endpoint for the evaluation of treatment efficacy will be event-free survival (EFS), defined as the time to disease progression, disease relapse, occurrence of a second neoplasm, or death from any cause, measured from the time of study enrollment, as well as from the start of radiation therapy for some analyses. For primary analyses, disease progression or recurrence occurring prior to radiation therapy will not be classified as events, although they may be so classified for selected secondary analyses. The secondary endpoint in this analysis is overall survival (OS), which is defined as the time to death.

14.4.2 Methods Of Analysis

Standard survival methods will be for analysis of EFS and OS. These include stratified and unstratified logrank tests and Cox regression analysis for assessing the association between outcome and patient and tumor characteristics, and the product-limit (Kaplan-Meier) estimate for estimation of EFS and OS probability. [64] Parametric survival methods will also be used where appropriate. [65]

14.4.3 Precision of Estimate of 5-Year EFS And OS

Based on a minimum of 250 patients with potential follow-up at least two years, estimates of 2-years EFS and OS for the entire cohort will have precision corresponding to maximum standard error of approximately ±3.2%. Estimates of 5-years survival at that time will have maximum standard error of approximately ±3.5%.

Interim monitoring for this analysis will be based on comparison of 2-years EFS in the overall cohort with the theoretical baseline of 70% EFS at 2 years. This baseline is determined from the analysis of a combined series of patients with newly diagnosed ependymoma from the CCG-9942 (N=84) and St Jude Children's Research Hospital (N=98). [20,37] Two year EFS in these two series was 70%±6% and 78%±6%, respectively. The combined estimate of two-year EFS is 74%±4%, with a lower 95% confidence bound of 67%. This analysis will be based on a Weibull parametric cure model. [66] The one-sided 80% upper profile likelihood confidence bound on two-year EFS from this model will be computed using Lan-Demets[64] type αt^2 spending function adjustment of the confidence level, where t is based on the appropriate information-time scale. A detailed review of the outcome in the entire cohort will be undertaken if the adjusted upper confidence bound is less than 70%, with consideration give to whether the treatment of the overall cohort of patients should be modified.

14.4.4 Estimate The 5-Year EFS in Differentiated, Supratentorial Ependymoma Who Undergo a Gross Total Resection And No Subsequent Treatment

Although the assumptions above, based on previous studies, projects a 30% failure rate in this subcohort, this is considered an unacceptable failure rate, and current expectations are that, with modern surgery, the overall failure rate in this group will be 10% or less in 5 years. Assuming that failure occurs approximately exponentially in the first 5 years, a lower, one-sided, 80% profile likelihood confidence bound on the exponential failure rate parameter will be the basis for analysis. If this lower bound exceeds a rate of 10% per 5 years, the outcome in this cohort will be considered unacceptable.

Interim monitoring for this analysis will be based the lower, one-sided confidence bounds with a Lan-Demets[67] type αt^2 spending function adjustment of the confidence level, where t is based on the appropriate information-time scale. A detailed review of the outcome in this cohort will be undertaken if the adjusted lower confidence bound exceeds the above acceptable rate, with consideration given to whether this treatment of this group of patients should be modified. This monitoring rule will serve as a guideline to the committee, and should not be interpreted literally as a charge to the committee to terminate or continue the study.

14.4.5 Estimate The Rate Of Gross-Total or Near-Total Resection With Second Surgery After Chemotherapy Treatment Among Patients With Initial Subtotal Resections

This analysis will be conducted separately in anaplastic and differentiated tumors, with 41 and 92 patients, respectively, expected in these groups. The standard error for the proportion of patients who achieve GTR/NTR after second surgery will be at most 0.078 and 0.052, respectively. A combined analysis will also be performed, the standard error for the proportion achieving GTR/NTR being at most 0.043. Additional analyses will include a comparison of survival in patients who achieve GTR/NTR with or by second surgery with those who had a GTR/NTR initially (with the realization that this comparison does not address the issue of whether delaying maximal initial surgery is a preferable treatment strategy) and also with the group that does not undergo second-stage GTR/NTR.

14.4.6 Compare EFS Between Centrally Reviewed Differentiated Ependymoma And Anaplastic Ependymoma Under The Prescribed Treatment Strategy

This analysis will be based on a log-rank comparison of EFS estimates in these two groups. Based on a two-sided log-rank test with Type I error 0.05, this comparison will have at least 80% power to detect a 16% larger 5-year EFS rate in patients with differentiated tumors compared to those with anaplastic tumors, based on minimum 2-years follow-up and 2.5%/year loss-to-follow-up. [64,68]

14.4.7 Analysis of Local Control and Pattern of Failure

Site of tumor progression will be documented and analyzed qualitatively and quantitatively according to the methods described under Evaluation Criteria (Section 15.3 Patterns of Failure Evaluation). For protocol patients with localized disease treated with conformal radiation, care will be taken to characterize tumor recurrence or progression as occurring within the target field or outside the target field (in-field, out-of-field, marginal). Approximately 100 patients of this type will be enrolled, of which approximately 30 will experience tumor progression. Hence, the standard error of the estimate of the proportion of failures that are local will have maximum standard error of ±9%. For patient treated with surgery alone, tumors will similarly be classified as occurring within or outside the original surgical field. However, fewer than 20 such patients are expected, of whom fewer than 5 will fail, so that no meaningful statistical analysis is possible.

14.4.8 Interim Monitoring of Tumor Progression During Chemotherapy

A total of 133 patients are expected to receive chemotherapy in this study. While tumor progression during chemotherapy in subtotally resected patients is expected to be unlikely, progression rates of 0.10 or lower are considered acceptable. Monitoring for progression during chemotherapy will be performed at approximately 6 month intervals, using a Bayesian rule based on the posterior distribution of the proportion of patients who progress, computed using a binomial distribution with a Beta (4,36) prior on the probability of progression. This prior has mean 0.10 and 95% of support between 0.03 and 0.21. The monitoring rule will be satisfied in the posterior probability that the progression rate is greater than 0.10 exceeds 95%. Operationally, this rule will be satisfied, for example, if 8/25, 11/50, 21/133 progressions are observed. A detailed review of the outcome in this cohort will be undertaken if the rule is satisfied, with consideration given to whether this treatment of this group of patients should be modified. This monitoring rule will serve as a guideline to the committee, and should not be interpreted literally as a charge to the committee to terminate of continue the study.

14.4.9 Interim Monitoring of Successful Second Surgery After Chemotherapy.

A total of 133 patients are expected to receive chemotherapy in this study. For the proposed strategy in this group of patients to be considered successful, at minimum 50% of patients should will either be rendered radiologically tumor-free by chemotherapy or be amendable to second surgery that results in minimum residual disease (GTR or NTR). Interim monitoring of this endpoint will be performed at approximately 6 month intervals, using a Bayesian rule based on the posterior distribution of the proportion of patients successfully achieve minimum residual disease, computed using a binomial distribution with a Beta (4,4) prior on the probability. This prior has mean 0.50 and 95% of support between 0.18 and 0.82. The monitoring rule will be satisfied in the posterior probability that the minimum residual disease rate is less than 0.10 exceeds 95%. Operationally, this rule will be satisfied, for example, if fewer than 7/25, 18/50, 57/133 successes are observed. A detailed review of the outcome in this cohort will be undertaken if the rule is satisfied, with consideration given to whether the treatment of this group of patients should be modified. This monitoring rule will serve as a guideline to the committee, and should not be interpreted literally as a charge to the committee to terminate or continue the study.

14.4.10 Analysis Of CGH-Detected Chromosome Aberrations And Their Relationship To Outcome And Histology

The analysis of chromosome aberrations in ependymoma and its relationship to histology and outcome will be by its nature exploratory. The statistical analysis of these data will require some care is appropriately controlling experiment-wise error rate. The preliminary analytic strategy will first to identify candidate aberrations of interest, and then to perform univariate comparisons of EFS and of reviewed histology (anaplastic vs differentiated) in patients with and without the aberrations. Nominal Type I error levels will be adjusted appropriately.

Assuming that at minimum 100 patients in this study will have CGH data, and that approximately 10 promising candidate gene aberrations are identified. Based on a two-sided logrank test with an overall Type I error rate of 5%, an individual gene aberration identified in approximately 50% of patients would need to correspond with approximately a 3.6-fold difference in failure rate between patients with and without the aberration (e.g., long-term EFS of 29% vs 71%) to be detectable with 80% power after adjustment for multiple comparisons. The detectable effect size will depend on the number of candidate aberrations and the proportions of patients in the sample associated with each aberration.

All genomic profiles generated will be available to all COG-authorized investigators through a web-based centralized microarray data repository developed and maintained by the COG Statistics Office in Arcadia. Expression profiles will also be available through a similar arrangement. Ultimately there will be an integration of the genomic and expression databases in order to facilitate the determination of possible correlation between expression profiles and chromosomal abnormalities.

The statistical approach in analyzing the genomic profiling data will be similar to those describe for the analysis of CGH data. Both univariate and multivariate analysis will be employed to detect possible correlation between copy number changes/LOH and histologic response or survival. In addition, for the purpose of building a molecular classification system, both supervised and unsupervised clustering strategies will be utilized for class discoveries. Supervised methods for distinguishing between two classes of tumors, e.g. survivors versus treatment failures, utilize the class membership of samples in deriving discriminants for distinguishing between the classes based on genomic profiles. Linear and nonlinear regression methods, classification and regression trees, neural networks are all supervised methods. Unsupervised methods are algorithms for identifying clustering of cases with regard to genomic profiles without utilizing information about class membership. Supervised methods are generally more powerful for deriving predictors of class membership. Unsupervised methods are useful for discovering patterns that may be of biological relevance, although under current treatment they may not be effective for predicting response to therapy or survival.

14.4.11 Analysis of Neuropsychological and Quality of Life Evaluations

The analysis of neuropsychological and quality of life parameters will be primarily descriptive. The value of this analysis will depend to a large extent on the ability to complete follow-up assessments in a large fraction of patients on this study. If the majority of patients are evaluated (e.g., 100 of the approximately 125 projected 5-year event-free survivors), this analysis will provide a very good description of the average neuropsychological profile of this cohort. In addition, with this sample size, one would be able to detect, with at least 80% power, a decrease in mean outcome in these patients from expected norms of 1/3 of the standard deviation in the reference population, based on a one-sided test, with 5% experiment-wise error rate. However, if a much smaller proportion of patients are assessed, then although the sample size may be nominally adequate, the possibility of selection bases may seriously compromise the value of these neuropsychological assessments.

14.5 Gender and Ethnicity Considerations

Review of outcome data from previous Ependymoma studies indicates that treatment effects are consistent between gender and ethnicity. That is, no one treatment examined has proven superior for one gender or ethnic group. Because of this, the study size will not be adjusted to ensure high power to detect differences in outcome in groups defined by ethnicity or gender. We will, however, contrast therapeutic outcomes in two situations: first, across subgroups defined by gender, viz., males v. females: Second, across subgroups defined by ethnicity, white v. black v. Hispanic.

Expected Accrual by Sex and Race/Ethnicity (Total N=250)

SEX/RACE	Black	Hispanic	White	Other	Total
Female	18	12	110	3	143
Male	12	18	73	3	107
Total	30	30	183	6	250

Projection based on CCG-9942 study of 83 pediatric ependymomas.

15.0 EVALUATION CRITERIA

15.1 This Study Will Utilize The CTC Version 2.0 For Toxicity And Performance Reporting

A copy of the CTC Version 2.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). Additionally, Grade 3 and 4 toxicities are to be reported via remote data entry (RDE).

15.2 Response Criteria

This study will use the (RECIST) Response Evaluation Criteria in Solid Tumor from the NCI as modified below.

15.2.1 Measurable Disease

The presence of at least one lesion that can be accurately measured in at least one dimension.

Serial measurements of lesions are to be done with MRI (predominately post-contrast T1 or T2-weighted imaging). The same method of assessment should be used to characterize each identified and reported lesion at baseline and during follow-up.

15.2.2 Quantification of Disease Burden
The sum of the longest diameter (LD) for all target lesions will be calculated and reported as the disease measurement.

15.2.3 Complete Response (CR)
Disappearance of all target lesions.

15.2.4 Partial Response (PR)
At least a 30% decrease in the disease measurement, taking as reference the disease measurement done to confirm measurable disease at study entry.

15.2.5 Progressive Disease (PD)
At least a 20% increase in the disease measurement, taking as reference the smallest disease measurement recorded since the start of treatment; or the appearance of one or more new lesions.

15.2.6 Recurrent Disease
Appearance of one or more new lesions.

15.2.7 Stable Disease (SD)
Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest disease measurement since the treatment started.

15.2.8 Response Assessment
Each patient will be classified according to their "best response" for the purposes of analysis of treatment effect. Best response is determined from the sequence of the objective statutes described above.

15.2.9 Best Response
Two objective status determinations of CR before progression are required for best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR. Two determinations of stable/no response or better before progression, but not qualifying as CR or PR are required for a best response of stable/no response; if the first objective status is unknown, only one such determination is required. Patients with an objective status of progression on or before the second evaluations (the first evaluation is the first radiographic evaluation after has been administered) will have a best response of increasing disease. Best response is unknown if the patient does not qualify for a best response of increasing disease and if all objective statuses after the first determination and before progression are unknown.

Use of the definition is illustrated in Table 1 with several sequences of objective statuses and the corresponding best response.

Table 1. Sequences of objective statuses with corresponding best response.

1st Status	2nd Status	3rd Status	Best Response
Progression			Increasing Disease
Stable, PR, CR			
Unk	Progression		Increasing Disease
Stable	Stable Progression		Stable
Stable, Unk	PR, CR	Progression	Stable
Stable, Unk	Unknown	Progression	Unknown
PR	PR	Progression	PR
PR	CR	Progression	PR
PR, CR	Unknown	Progression	Unknown
CR	CR	Progression	CR
Unknown	Stable	Progression	Stable

The best response is the same if these sequences are preceded by the objective statuses of unknown or stable or if unknowns separate the first objective status from the second.

15.3 Patterns of Failure Evaluation

The patterns of failure for patients with localized ependymoma may be described as local, distant or a combination of local and distant and are based primarily on imaging evaluation of the neuraxis. Local failure is defined as progression of known residual tumor or the appearance of tumor at known prior sites of disease that were at some point without evidence of disease. Distant failure is defined as the appearance of tumor at sites other than known prior sites of disease. Distant failure most often occurs in the subarachnoid space and may occur at any point within the neuraxis. Combined local and distant failure is defined when evaluation of the entire neuraxis reveals local and distant failure. The present study involves treatment of the primary site only and 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 of this protocol will be higher than that observed for patients treated with conventional radiation therapy using the same prescription dose and a larger volume. If the treatment volume did not include the entire area at risk one would expect an increase in the rate of failure and a change in the pattern of failure with local failure as a component of failure occurring at a higher than expected rate. The monitoring of EFS will assess the rate of failure. 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. [20] 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. [69] 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 significant 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.

16.0 ADVERSE EVENT REPORTING REQUIREMENTS

16.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents.

16.2 Determination of Reporting Requirements

Reporting requirements may include the following considerations: 1) the characteristics of the adverse event including the *grade* (severity); 2) the *relationship to the study therapy* (attribution), and 3) the *prior experience* (expectedness) of the adverse event;

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. In some cases an agent obtained commercially may be used for indications not included in the package label. In addition, NCI may on some occasions distribute commercial supplies for a trial. Even in these cases, the agent is still considered to be a commercial agent and the procedures described below should be followed.

Determine the prior experience Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected,* for reporting purposes only, when either the type of event or the severity of the event is not listed in:

- ***the current NCI Agent-Specific Adverse Event List (provided in the Drug Information Section of this protocol); or***
- ***the drug package insert (for treatments with commercially available agents).***

16.3 Reporting of Adverse Events for Commercial Agents - AdEERS abbreviated Pathway

Commercial reporting requirements are provided in Table B. The commercial agent(s) used in this study are listed in the Drug Information Section of this protocol.

- COG requires the AdEERS report to be submitted **within 5 calendar days** of learning of the event.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Table B

Reporting requirements for adverse events experienced by patients on study who have NOT received any doses of an investigational agent on this study.

AdEERS Reporting Requirements for Adverse Events That Occur During Therapy With a Commercial Agent or Within 30 Days[1]

Attribution	Grade 4		Grade 5
	Unexpected	Expected	
Unrelated or Unlikely			AdEERS
Possible, Probable, Definite	AdEERS		AdEERS

[1]This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent which can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via AdEERS.

16.4 **Reporting Secondary AML/MDS**

All cases of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) that occur in patients on NCI-sponsored trials following their chemotherapy for cancer must be reported to the Investigational Drug Branch (IDB) of the NCI Cancer Therapy Evaluation Program (CTEP) and included as part of the second malignant neoplasm reporting requirements for this protocol (see data submission packet). Submit the following information within two weeks of an AML/MDS diagnosis occurring after treatment for cancer on NCI-sponsored trials:

- a completed NCI/CTEP Secondary AML/MDS Report Form *(do not use AdEERS);*
- a copy of the pathology report confirming the AML/MDS; and
- a copy of the cytogenetics report (if available).

Submit the information via fax to:

NCI (fax # 301-230-0159) and

COG (fax # 626-445-6715; attention AE Coordinator)

Note: If a patient has been enrolled in more than one NCI-sponsored study, the NCI/CTEP Secondary AML/MDS Report Form must be submitted for the most recent trial. The COG must also be provided with a copy of the report even if the study was not the patient's most recent trial.

17.0 RECORDS AND REPORTING

17.1 Categories Of Research Records

Research records for this study can be divided into three categories:

1. Reference Labs, required reports and QARC data. These data accompany submissions to these centers, which forward their review data electronically to the COG Statistics and Data Center.

2. Non-computerized information: Roadmaps, Pathology Narrative Reports, Surgical Reports. These forms are faxed to the Statistics and Data Center at (626) 445-4334.

3. Computerized Information Electronically Submitted: All other computerized data will be entered on the C.O.G. Remote Data Entry System with the aid of schedules and worksheets (essentially paper copies of the RDE screens) provided in the data form packet.

See separate Data Form Packet posted on the COG website which includes submission schedule.

17.2 CDUS

This study will be monitored by the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. This is not a responsibility of institutions participating in this trial.

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SAMPLE INFORMED CONSENT

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document which are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they must be justified in writing by the investigator and approved by the IRB.

ACNS0121, A Phase II Trial of Conformal Radiation Therapy For Pediatric Patients With Localized Ependymoma, Chemotherapy Prior to Second Surgery for Incompletely Resected Ependymoma and Observations for Completely Resected, Differentiated, Supratentorial Ependymoma

WHAT IS THIS STUDY ABOUT?
This study is a clinical trial (a research study involving human patients). Clinical trials only include patients who choose to take part. Please take your time to make your decision. Discuss your decision with your friends and family.

This study is being carried out by the Children's Oncology Group (COG). COG is an international research group that consists of more than 200 hospitals that treat children with cancer in the United States, Canada, Australia, and Switzerland. It is common medical practice to treat children with cancer on international research studies like this one.

You are being asked (to allow your child) to take part in this study because you have (your child has) a type of brain tumor called an ependymoma. Standard treatment for ependymoma includes surgery to remove as much of the tumor as possible, and radiation therapy (the use of high-dose x-rays to kill cancer cells).

Previous experience has shown that when ependymoma is not completely removed surgically, the outlook with standard treatment is poor. This study will include chemotherapy (treatment with anti-cancer drugs) as part of treatment for patients whose tumors are not completely removed surgically. These patients may undergo a second surgery to remove more tumor. All patients will then receive conformal radiation therapy.

Patients with complete or nearly complete surgical removal of tumor will be given conformal radiation therapy without chemotherapy.

The standard way of giving radiation therapy uses two radiation beams pointed at the tumor. The radiation beams are usually larger than the actual tumor, so that the area around the tumor also receives radiation. This is done to make sure that the radiation reaches all of the tumor. With the help of computers, we are now able to use MR images and CT scans to plan the treatment, whereas before we could only estimate where the tumor was located. You are being asked to allow your child to take part in a research study looking at a new way of giving radiation therapy, called 3-dimensional conformal radiation therapy. This treatment is designed to give radiation to the tumor, but to a much smaller area of normal brain tissue around the tumor. The treatment has been used recently to treat many children with cancer. Because we do not know if treating a smaller area with radiation will increase the chance that the tumor will come back, this is a research study.

Patients with ependymoma in the upper part of the brain and whose tumors have undergone complete surgical removal will only be observed after surgery if the pathologists determine that the tumor does not have aggressive features.

The exact cancer treatment each patient receives will depend on the location of the tumor, how much of the tumor is removed after surgery, and the way the tumor tissue looks under a microscope (histology).

Children under the age of 3 years: This protocol uses radiation therapy after surgery in children under the age of 3 years which is a change from the approach that has been used in the past where chemotherapy was used to delay radiation therapy because of concerns about side effects. This change has been made because of the poor results achieved when chemotherapy was used to delay radiation therapy and because radiation therapy may be safer when used according to the guidelines developed for this protocol. The possible risks associated with radiation therapy are explained in this consent form and are considered to be acceptable even for the youngest children. The benefit for younger children receiving radiation therapy earlier is the opportunity to improve their chances of controlling the tumor.

An outline of the possible treatment plans is given later in this consent.

WHY IS THIS STUDY BEING DONE?
The goals of this study are:

- **To look at the progress of patients who are observed after surgery that successfully removes the entire tumor.**

- **To look at how many patients, who receive chemotherapy, have their remaining tumor successfully removed by a second surgery.**

- **To look at the progress of patients that are given conformal radiation therapy after surgery.**

- **To determine if conformal radiation therapy can be used instead of standard radiation therapy and to study the effect of radiation on learning, thinking, hearing and the production of hormones (substances made in the brain that affect growth and development.**

- **To look at the influence of tumor grade on tumor progression after conformal radiation therapy.**

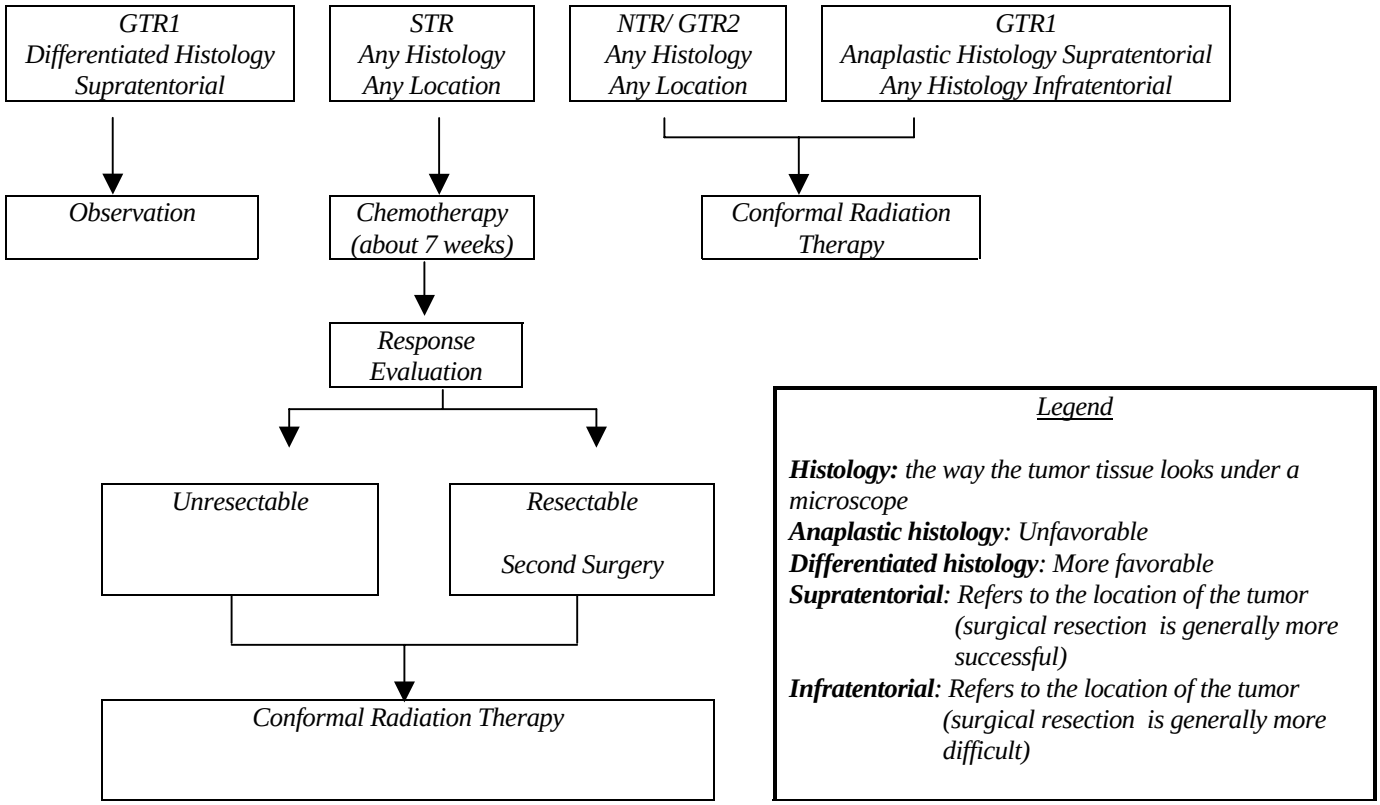
- **To study tumor tissue for possible genetic factors related to ependymoma.**

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
There will be about 250-350 patients participating in this study.

WHAT WILL HAPPEN TO ME (MY CHILD) ON THIS STUDY?
Before beginning treatment on this study you (your child) will have surgery to remove as much of the brain tumor as possible. As described earlier, each patient's treatment will depend on the location of the tumor, how much of the tumor is removed after surgery, and the way the tumor tissue looks under a microscope (histology). Below is an outline that describes the possible treatment plans.

Extent of Resection
GTR1 (gross total resection 1): No remaining tumor visible by microscope and no evidence of disease visible on scans taken after surgery.
GTR2 (gross total resection 2): Remaining tumor visible by microscope and no evidence of disease on scans taken after surgery.

NTR (near total resection): Remaining tumor measuring less than or equal to 5 mm in greatest dimension visible on scans taken after surgery.
STR (subtotal resection): More than 5 mm of remaining tumor visible on scans taken after surgery.



Treatment
If you are (your child is) to be given chemotherapy, chemotherapy will start 2 weeks after entering the study. The chemotherapy will be given in 2 cycles over 7 weeks.

Cycle A: The first cycle, Cycle A, is 3-weeks long and consists of the anti-cancer drugs vincristine, carboplatin, and cyclophosphamide. The drug Mesna will also be given to protect the bladder from possible damaging effects and the drug filgrastim will be given to help the body recover.

Vincristine: Will be given directly into a vein on Days 1 and 8 of Cycle A.
Carboplatin: Will be given directly into a vein for 1 hour on Day 1 of Cycle A.
Cyclophosphamide: Will be given directly into a vein for 1 hour on Days 1 and 2 of Cycle A.
Mesna: Will be given on the following schedule: 1) initially directly into a vein with cyclophosphamide continuously for 1 hour 2) after the cyclophosphamide infusion continuously for 3 hours, and 3) After the 3 hour infusion another dose administered over 15 minutes.
Filgrastim: Will be given directly into a vein, or injected under the skin, every day, starting Day 3 until your (your child's) blood tests show that the you (your child) has recovered.

Cycle B: This cycle will last about 4 weeks and will start when you (your child) recover(s) from Cycle A. The following anti-cancer drugs are given during Cycle B: Vincristine, Carboplatin, and Etoposide.

Vincristine: Will be given directly into a vein on Days 1 and 8 of Cycle B.
Carboplatin: Will be given directly into a vein for 1 hour on Day 1 of Cycle B.
Etoposide: Will be given by mouth every day, Days 1-21 of Cycle B.

Radiation Therapy

If you (your child) is receiving radiation therapy, it will be given to the brain once a day, 5 days a week. The total number of radiation therapy days will depend on the amount of tumor remaining after surgery, as well as your (your child's) age. Most patients will receive a total of 33 treatments. Each treatment will take 20 minutes to 1 hour. Children less than 18 months at the time of conformal radiation therapy who have most if not all of the tumor removed will receive fewer treatments.

Conformal radiation therapy will be given on this study. That means that the radiation oncologist will use a technique that focuses most of the radiation energy on the tumor, with less energy directed at the areas surrounding the tumor. This technique is being used to limit the side effects of radiation therapy. Side effects are unintended results of treatment. Possible side effects of radiation therapy to the brain are listed later in this consent.

Second Surgery

If you are (your child is) given chemotherapy, you (your child) will be evaluated for the possibility of a second surgery after the completion of chemotherapy. If you are (your child is) not given a second surgery after chemotherapy, you (your child) will start conformal radiation (described above). If you are (your child is) given a second surgery after chemotherapy, you (your child) will be given conformal radiation therapy after surgery.

Standard Medical Tests

Before treatment on this study begins, and while receiving treatment, you (your child) will be given a series of standard medical tests:

- Physical exam
- Blood tests
- Urine tests
- Tests of brain function #
- Tests of liver function
- Hearing tests
- Magnetic Resonance Imaging (MRI) of brain and spine. (MRI uses magnetic waves to look at soft tissues of the body.)
- Spinal tap*
- Eye exam

**Spinal Tap:* In most cases, you (your child) will get medications to numb the pain and blur the memory. A small area of skin over the back will be cleaned and numbed with Emla cream and/or lidocaine. A small needle will be inserted between the spine bones and into the spinal fluid and a few teaspoons of spinal fluid will be collected. Spinal taps may cause headache. The test is painful and has a small risk of infection or bleeding. The pain usually gets better within seconds to hours.

Because treatment and the tumor itself can cause problems with learning and thinking you (your child) will receive a series of "neuro-psychological exams" which are like IQ tests during treatment and follow-up. The testing will take approximately 1 to 2 hours.

Some of the tissue already taken and copies of the films used to make the diagnosis of your disease will be sent to central review centers as part of COG quality control.

If you (your child) is designated to be observed after surgery they will not receive radiation therapy or chemotherapy. They will be followed regularly with MRI and other tests. The benefit of observing patients is that they will avoid the potential side effects of radiation therapy. The risk associated with this approach is that the tumor will recur and that surgery may not be possible or that the tumor will recur and spread throughout the brain and spine. It has been the practice of some doctors not to give any additional treatment, including radiation therapy, to children with ependymoma when the tumor has been completely removed. The investigators who designed this protocol have created strict measures to choose those who will not receive additional treatment after surgery and careful follow-up to minimize the risks to those who are designated for observation.

HOW LONG WILL I (MY CHILD) BE ON THIS STUDY?
You (your child) will be treated on this study for as little as a few weeks to as long as 6 months. However, you (your child) will continue to have physical exams, blood tests, hearing tests, tests of liver function, tests of brain function, and MRIs for a minimum of 5 years so that researchers can continue to observe any effects of treatment. The protocol suggests that follow-up should continue beyond 5 years. After treatment, subjects will have follow-up examinations and medical tests. We will continue collect some medical information about how you are doing for 10 years after the last subject starts the study.

The researchers may decide to take you (your child) off the study if your (your child's) cancer gets worse or you (your child) experiences side effects from the treatment that are considered too severe.

You can leave (remove your child from) the study at any time. However, if you consider leaving (removing your child from) the study, we encourage you to talk to your (your child's) regular physician and to the research physician before making a final decision.

WHAT ARE THE RISKS OF THE STUDY?
Chemotherapy agents are drugs that, in addition to killing tumor cells, can damage normal tissue. These drugs, however, have been in use long enough so that severe problems can usually be avoided. Side effects are usually reversible when medication is stopped but occasionally can persist and cause serious complications. The common side effects from cancer treatment include nausea, vomiting and hair loss. Drugs may be given to prevent or counteract nausea and vomiting but sometimes these symptoms may be severe enough that you (your child) will need to have fluid given directly into the vein to replace the fluid loss. Hair loss is usually temporary but on rare occasions it may be permanent. The more serious side effect from cancer treatment is depression of the number of blood cells resulting in anemia, increased chance of infection and bleeding tendency. These complications can sometimes be fatal. Blood tests will be done to monitor your (your child's) progress.

You (your child) may receive all or some of the following drugs in this protocol. The following kinds of side effects may be observed from the drugs used in this protocol:

Risks and side effects related to carboplatin include those which are:

Likely	Less Likely	Rare but serious
• Nausea and vomiting • fewer red blood cells and white blood cells and platelets in the blood o a low number of red blood cells can make you feel tired and weak o a low number of white blood cells can make it easier to get infections o a low number of platelets causes you to bruise and bleed more easily • Abnormal levels of certain salts in the body like sodium and potassium	• Allergic reactions (can be severe and life-threatening causing difficulty in breathing and or a drop in blood pressure) • Rash • Metallic taste • Numbness and tingling in the fingers and toes • Hair loss • Constipation or diarrhea • Pain in your abdomen • Temporary changes in vision • Damage to the ear causing hearing and balance problems • A feeling of weakness and/or tiredness • Inflammation and/or sores in the mouth (and/or throat and /or esophagus, the tube that leads from the mouth to the stomach) that may make swallowing difficult and are painful (painful mouth sores)	• Damage to the liver • Damage to the kidney • Leukemia later in life

Risks and side effects related to <u>cyclophosphamide</u> include those which are:

Likely	Less Likely	Rare but serious
• Loss of appetite • Nausea • Vomiting • Fewer white blood cells in the blood. ○ A low number of white blood cells may make it easier to get infections. • Hair loss • Decreased ability of the body to fight infection • Absence or decrease in the number of sperm which may be temporary or permanent which may decrease the ability to have children	• Abnormal hormone function which may lower the level of salt in the blood • Abdominal pain • Diarrhea • Fewer red blood cells and platelets in the blood ○ A low number of red blood cells may make you feel tired and weak. ○ A low number of platelets may cause you to bruise and bleed more easily. • Bleeding and inflammation of the urinary bladder • Absence or decrease monthly periods which may be temporary or permanent and which may decrease the ability to have children • Temporary blurred vision • Nasal stuffiness with IV infusions • Skin rash • Darkening of areas of the skin and finger nails • Slow healing of wounds • Infections	• Heart muscle damage which may occur with very high doses and which may be fatal • Abnormal heart rhythms • Damage and scarring of lung tissue which may make you short of breath • A new cancer or leukemia resulting from this treatment. • Damage or scarring of urinary bladder tissue • Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever • Infertility which is the inability to have children

Risks and side effects related to etoposide include those which are:

Likely	Less Likely	Rare but serious
• Nausea and vomiting • Hair Loss • A feeling of weakness or tiredness • fewer red and white blood cells and platelets in the blood o a low number of red blood cells can make you feel tired and weak o a low number of white blood cells can make it easier to get infections o a low number of platelets causes you to bruise and bleed more easily	• Loss of appetite • Decreased blood pressure during the infusion which may require treatment • rashes • Diarrhea • Pain in the abdomen • Mouth sores • Tingling sensation or loss of sensation in fingers or toes • A feeling of extreme tiredness or weakness • The finger or toe nails may loosen from their nail beds • Inflammation of the vein through which the medication was given • Chest pain	• Damage to the liver • Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever • A new cancer or leukemia resulting from this treatment • Severe rashes which can result in loss of skin and damage to mucous membranes • Absence or decrease monthly periods which may be temporary or permanent and which may decrease the ability to have children • Damage to the heart muscle which may make you feel tired, weak, feel short of breath, and retain fluid

Risks and side effects related to Filgrastim (G-CSF) include those which are:

Likely	Less Likely	Rare but serious
• Aching or pain in the bones	• Local irritation at the site of the injection • Headache • Higher than normal levels of liver enzymes which may indicate liver irritation or damage and uric acid in the blood • A low number of platelets in the blood which may cause you to bruise and bleed more easily • Low fever • Enlargement of the spleen which may cause pain in the abdomen or left shoulder • Worsening of skin rashes • Inflammation of a blood vessel in the skin leading to a raised purple rash and bruising • Higher than normal white blood count	• Allergic reactions which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, hives and facial swelling. This reaction is very rare and has been associated mainly with intravenous administration. • If you are known to have sickle cell disease, filgrastim may cause a sickle cell crises. • Severe damage to the spleen (an organ in the abdomen/belly which stores blood cells) which could lead to pain and loss of blood into the abdomen (belly) and maybe life threatening • Difficulty breathing and lung damage that may be due to the white blood cells that are stimulated by filgrastim traveling to the lungs when they are inflamed or infected. • A blood disorder or leukemia that has only been seen in patients with certain immune disorders who are treated for a very long time.

Risks and side effects related to MESNA include those which are:

Likely	Less Likely	Rare but serious
• Bad taste when taken by mouth.	• Nausea. • Vomiting • Stomach pain. • Headache. • Pain in arms, legs and joints. • Tired feeling. • Rash. • Temporary low blood pressure. • Diarrhea. • Fever • Facial flushing with red cheeks • Nervousness • Dizziness • Confusion • Swelling around the eyes • Coughing • Rapid heart rate	• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, chills and fever

Risks and side effects related to vincristine include those which are:

Likely	Less Likely	Rare but serious
• Hair loss • Reversible nerve problem that may affect the way you walk or the feelings in your fingers or toes • Constipation	• Jaw pain • Headache • Muscle Weakness • Pain and bloating in your abdomen • Numbness and tingling • Wrist or foot drop • Drooping eyelids • Double vision, difficulty seeing at night • Abnormal walk with foot slapping • Difficulty with urination or increase desire to urinate • Dizziness • A mild drop in white blood cells, red blood cells and platelets in the blood o a low number of red blood cells can make you feel tired and weak o a low number of white blood cells can make it easier to get infections o a low number of platelets causes you to bruise and bleed more easily	• Complete stoppage of your intestinal activity which can result in intestinal blockage • If the drug leaks out of the vein when being administered it will cause damage to nearby tissue • Seizures • Vocal cord paralysis • Difficulty breathing • Inability to walk • Decreased ability to hear clearly

Reproductive Risks

Because the drugs in this study can affect an unborn baby and risks due to radiation are unknown to an unborn or nursing child, you (your child) should not become pregnant or father a baby while on this study. You (Your child) should not nurse your baby while on this study. Ask about counseling and more information about preventing pregnancy.

Radiation Risks

All types of radiation therapy have side effects. Some side effects depend on the location of the tumor. Some go away during or soon after treatment (short-term effects), and others may appear later (long-term effects). In addition, the side effects of radiation can be made worse by other treatments that are given (surgery, chemotherapy, or other medicine). There may be side effects that we do not know about yet. The list below gives possible short-term and long-term side effects.

Short-term: **Possible short–term side effects of radiation therapy include nausea and vomiting; fatigue (tiredness) and loss of appetite; irritation or redness of the skin and hair loss corresponding to the entrance and exit points of the radiation beams; rarely there is peeling of the skin at the site of irradiation; if the ear canal or middle ear receives a significant doses there may be an increase in the amount of ear wax (cerumen), there may also be a feeling of fullness that may last for weeks or months although this should be uncommon; in general, blood counts are not reduced by treatment of small volumes of the brain, for those children who have received chemotherapy and G-CSF prior to radiation therapy there may be a transient lowering of counts during treatment although this would most likely be due to the prior chemotherapy. Hospitalization should not be required during radiation therapy. In the event that you (your child) requires general anesthesia or sedation during radiation therapy, the short term side effects of treatment listed above may be slightly worse including fatigue and loss of appetite.**

Long-term: **The occurrence and severity of long-term side effects of radiation therapy to the brain depend on the age of the patient at the time of treatment, the area of the brain that requires treatment, complications that arise from the tumor or treatments prior to radiation therapy such as surgery and chemotherapy. Growth hormone deficiency after radiation therapy is common. Less common are deficiencies in thyroid hormone, stress (adrenal) hormone, and the hormones required for puberty. Any type of hearing loss after radiation therapy alone occurs only in the minority of cases and many years after treatment. Combined with chemotherapy, such as that used in this study for specific patients, hearing loss maybe seen within one to two years after radiation therapy. Radiation therapy may affect the ability to learn and generally speaking, overall performance in school. Radiation therapy may also affect growth and development by decreasing the growth of bone and soft tissues that are in the field of treatment. Permanent hair loss occurs rarely. The doses of radiation used in this study are generally accepted as safe meaning that the chance of breakdown of normal tissue (necrosis) or significant blood vessel damage that would result in stroke or permanent neurologic damage is very rare. With any type of radiation therapy there is always the chance that another tumor may appear years later in tissues that are in the field of radiation.**

WILL I (MY CHILD) BENEFIT FROM THIS STUDY?
There may or may not be direct medical benefits to you (your child) from taking part in this study. It is hoped that treating a smaller volume will reduce side effects of radiation therapy and that chemotherapy, if required, will make the tumor more resectable. It is also hoped that the information learned from this study may help future patients with brain tumors.

ARE THERE OTHER TREATMENT OPTIONS?
Yes, there are other options.

- **The standard treatment for ependymoma, which is surgery and conventional radiation therapy.**
- **Another experimental treatment (if available).**

Please discuss these options with your regular doctor as well as other trusted personal and family advisors.

WILL MY (MY CHILD'S) RECORDS BE CONFIDENTIAL?
We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

It is very unlikely that the research testing will uncover important information about you or your current or future health. If this unlikely event occurs, the researchers may contact your doctor through Children's Oncology Group about what the test results might mean. Only your doctor will be notified and the information will remain confidential. Your doctor would discuss this unexpected finding with you, and may recommend consultation with a genetic counselor and/or repeat testing in a clinical (not research) laboratory if necessary. It is possible that your doctor may recommend that no additional action is necessary.

The Children's Oncology Group has a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. Information about the certificate is attached at end of this consent.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- **The Children's Oncology Group**
- **Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA), and Other U.S. and international governmental regulatory agencies involved in keeping research safe for people**
- **The Institutional Review Board of this hospital (IRB)**

WILL I HAVE TO PAY FOR THIS TREATMENT?
Taking part in this study may lead to added costs to your insurance company. Please ask about any expected added costs or insurance problems.
In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.
You will receive no payment for taking part in this study.

WHAT ARE MY (MY CHILD'S) RIGHTS AS A STUDY PARTICIPANT?
Taking part in this study is voluntary. You may choose (for your child) not to participate in this study. If you decide not to (let your child) participate, you (your child) will not be penalized and you (your child) will still receive the standard treatment.

If you choose to (allow your child to) participate, you may discontinue your (your child's) participation in the study at any time. If you discontinue participation in the study, physicians and hospital personnel will still take care of you (your child).

You also have the right to know about new information that may affect your (your child's) health, welfare, or your willingness to (let him/her) participate in the study. You will be provided with this information as soon as it becomes available.

Whether you participate or not, you (your child) will continue to get the best medical care this hospital can provide.

WHAT IF I HAVE QUESTIONS OR PROBLEMS?
For questions about the study or an injury related to the research, please call

_____ _____
NAME at TELEPHONE NUMBER

For questions about you rights as a study participant, please call

_____
NAME OF INSTITUTIONAL REVIEW BOARD REPRESENTATIVE*

at _____
TELEPHONE NUMBER

*The Institutional Review Board is a group of people who review the research study to protect your rights.

WHERE CAN I GET MORE INFORMATION?
The **COG Family Handbook for Children with Cancer** has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources. Your doctor can get you this Handbook, or you can get it at www.curesearch.org.

Visit the *NCI's Web site* at http://www.nci.nih.gov/cancerinfo/

If you are in the United States, you may call the NCI's *Cancer Information Service* at:
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

Information about long term follow-up after cancer treatment can be found at http://www.survivorshipguidelines.org/

You will get a copy of this form. You may also ask for a copy of the protocol (full study plan).

Use of Test Samples and Results for Related Studies
We are also asking your permission to save tumor tissue that is left over from surgical procedures, genetic material isolated from the tumor, and blood samples in a special tumor bank. The banked tumor and blood samples can be used for future research studies. Doctors and other medical scientists want to find better ways to detect cancers early and to treat, and if possible, cure patients who have them. To do this, they need more information about the characteristics of childhood cancers. They want to study samples of tumor tissue and blood to look for these characteristics.

Samples of your (your child's) tumor and blood will be sent to tumor banks designated by the COG such as the COG Biopathology Center in Columbus, Ohio. Participants' names will not be used for storing samples in the bank. The samples will be identified by a code. Samples will be frozen and stored in a carefully controlled deep freezer. There is no way to predict exactly what tests will be performed with the banked samples.

Future research tests could reveal new information about your (your child's) cancer, cancer in general, or even other medical disorders. The results of these research studies will not be disclosed to you or your (your child's) doctor. There will be no cost to you for any tissue collected and banked. You will not be paid for allowing your (your child's) leftover tissue to be used in research, even though it is possible that new cancer tests or treatments may be developed as a result of the research. The choice to let us bank the leftover tissue for future research is up to you. No matter what you decide to do, it will not affect your (your child's) care.

The genetic make-up of you or your child could be determined from the studies performed on the tissue samples undergoing research tests. These tests may identify genetic abnormalities that could now or in the future represent susceptibility to other diseases or conditions. This information will not be made available to you or your physician because these tests are considered research and are not certified for routine use. If this information were to be obtained by an unauthorized party such as an insurance company it could be used to deny you insurance coverage or affect you in a variety of other ways. The tumor bank, COG and researchers involved in this protocol protect your confidentiality by coding the tissues and information about you (your child) and by limiting access to the tissues and results from the research tests to authorized personnel.

If you decide now that your (your child's) tissue can be kept for research, you can change your mind at any time. Just contact your (your child's) doctor and let him or her know that you do not want your (your child's) tissue banked for research purposes, and the tissue will be destroyed.

Tumor tissue will be obtained at the time of surgery to make an accurate diagnosis, to determine the best course of treatment, and to obtain information about your tumor. This is often a part of regular care for ependymoma and may be done even if you do not join this study. Any remaining tumor sample will be used for molecular genetic studies (as part of this study). Any additional remaining tumor will be stored and made available for other biology studies of ependymoma. If you agree, any remaining tumor sample that is not needed for clinical diagnostic purposes and the specific research tests described in the study will be saved in the tissue bank.

We hope the information learned from the optional research tests will benefit other patients with ependymoma in the future.

There is no charge for the banking of tumor tissue and blood samples.

Refusal to participate in this banking study or withdrawal from the study will not jeopardize the medical care you (your child) will receive.

Now, please read the instructions below. After you understand each instruction, initial the answer that is right for you.

Instruction 1. Initial **YES** if you agree to let someone use some of the cells or tissue that we took from you (your child) at the time of a procedure to learn about, prevent, or treat cancer. Initial **NO** if you do not want your (your child's) sample (s) used for research about cancer.

1 YES_____ NO_____ (initials)

Instruction 2. Initial **YES** if you agree to let someone use the cells or tissue that we took from you (your child) at the time of the procedure to do research addressing medical questions other than those related to cancer. Initial **NO** if you do not want the sample(s) used for research addressing other questions.

#2 YES_____ NO_____ (initials)

Instruction 3. Initial **YES** if you would be willing to have a contact you at some time in the future about taking part in more research. Initial **NO** if you do not want someone to contact you about taking part in more research.

#3 YES_____ NO_____ (initials)

STATEMENT OF CONSENT

I have already read the above information. I have asked all my questions and I have gotten answers. I agree to enroll (my child) in this study.

A copy of this consent form will be provided to me

PATIENT NAME _____

_____ _____
SIGNATURE OF PATIENT DATE

_____ _____
SIGNATURE OF PARENT OR GUARDIAN DATE

_____ _____
SIGNATURE OF PHYSICIAN OR RESPONSIBLE INVESTIGATOR DATE

Attachment: Information about the Certificate of Confidentiality

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, you may choose to voluntarily disclose the protected information. For example, if you request the release of information in writing, the Certificate does not prevent that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.