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CHILDREN'S ONCOLOGY GROUP

ACNS1123

Phase 2 Trial of Response-Based Radiation Therapy for Patients with Localized Central Nervous System Germ Cell Tumors (CNS GCT)

A Groupwide Phase II Study

STUDY CO-CHAIRS

For Statistics and Data Center Contact Person see: http://members.childrensoncologygroup.org

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[redacted]

AGENT	NSC#	IND #
Carboplatin	241240	Exempt
Etoposide	141540	Exempt
Ifosfamide	109724	Exempt
Filgrastim (G-CSF)	614629	Exempt
Mesna	113891	Exempt

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ABSTRACT

Primary intracranial germ cell tumors (GCTs) represent 3-5% of all central nervous system (CNS) tumors and occur most commonly in the pineal and suprasellar region with a male preponderance. Germinomas account for approximately two-thirds of intracranial GCTs and the remaining third are non-germinomatous germ cell tumors (NGGCTs). [1-4] NGGCTs include endodermal sinus tumor or yolk sac tumor (YST), choriocarcinoma (CC), embryonal carcinoma (EC) and more commonly mixed malignant germ cell tumors. GCTs may secrete measurable proteins into the blood and/or cerebro-spinal fluid (CSF). Human chorionic gonadotropin-beta (hCGβ) and alpha-fetoprotein (AFP) are internationally used for diagnostic purposes. [1,5-7] Moderate elevation of hCGβ only in serum and/or CSF with characteristic neuroimaging features is considered diagnostic for bifocal germinoma and a biopsy is generally not mandated. Abnormal AFP levels and/or hCGβ levels in the serum or CSF >50 mIU/mL are generally considered to be consistent with NGGCTs and a biopsy is not required for diagnosis. However, biopsied germinomas have been reported to secrete hCGβ levels of up to 200 mIU/mL with no adverse impact upon survival. [8,9] Surgery/tissue biopsy is required for diagnosis in the absence of tumor marker elevation.

The late effects of craniospinal radiation (CSI) have long been recognized, particularly in children. Long-term sequelae include auditory and visual impairment, endocrine and neurocognitive dysfunction and secondary malignancies. [23-25, 10-14]

This protocol aims to reduce treatment burden in select groups of CNS GCTs, that is, localized NGGCT and germinoma. Localized disease as defined by this study includes tumors involving the suprasellar region, pineal region, both (bifocal), or elsewhere within the ventricles.

The objective of this study is to investigate whether pre-radiation therapy followed by response based radiation therapy (RT) will yield a high progression free survival (PFS) while reducing the

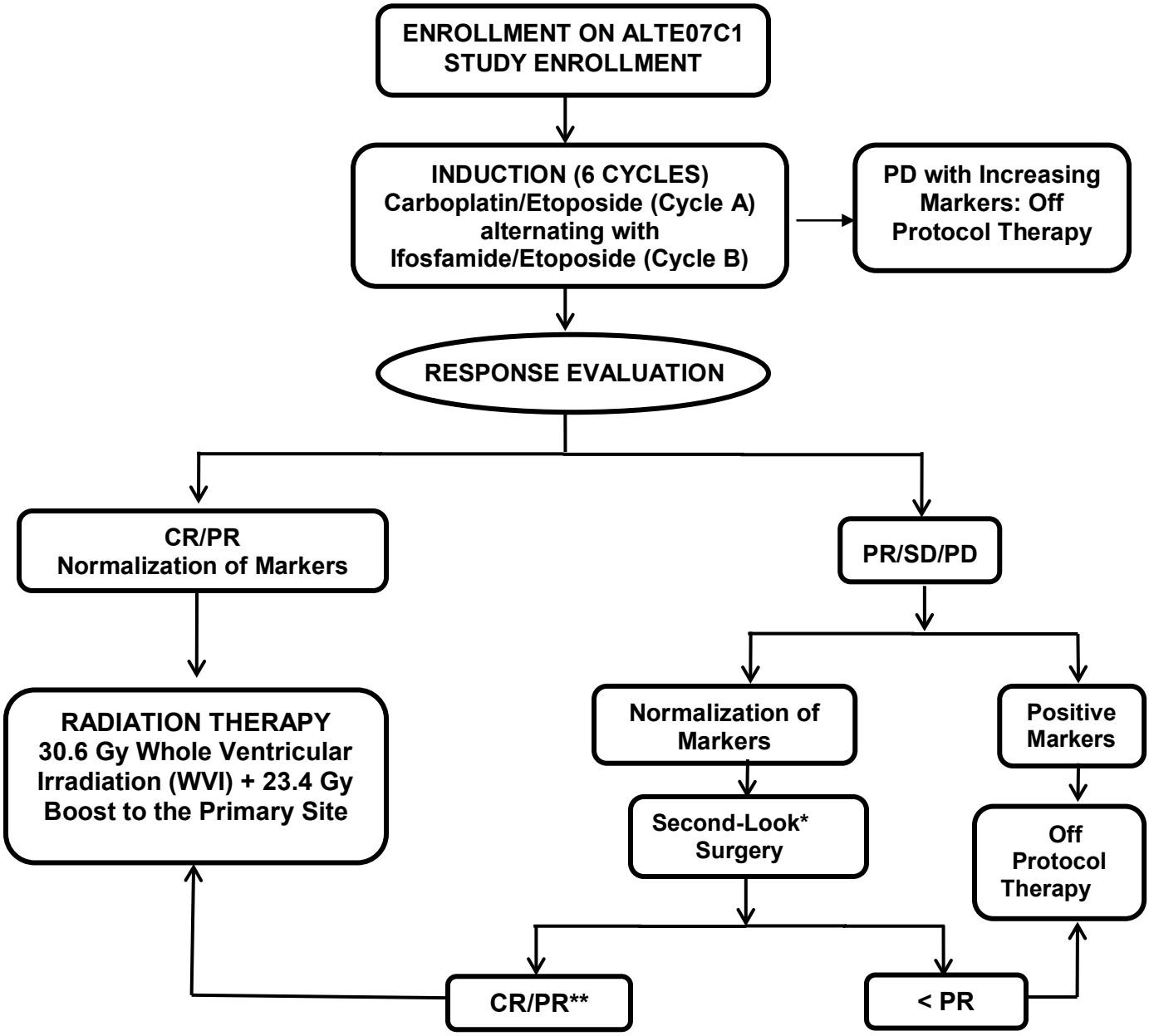
risk of long term neurocognitive sequelae and maintaining quality of life (QoL). Cognitive, social, emotional and behavioral functioning will be evaluated and longitudinally modeled for all patients (on both strata) using the ALTE07C1 protocol.

This study consists of 2 treatment strata: Stratum 1 for patients with localized NGGCTs and Stratum 2 for patients with localized germinomas. Treatment for NGGCTs (Stratum 1) will determine, as measured by the 3-year progression-free survival (PFS) rate, whether dose and volume of irradiation can be safely reduced to 30.6 Gy whole ventricular field irradiation (WVI) and 23.4 Gy primary site boost in the subgroup of children and young adults (ages 3-21 yrs) with localized NGGCT who have a magnetic resonance imaging (MRI) confirmed complete response (CR) or partial response (PR) in response to induction chemotherapy and negative serum and cerebrospinal fluid (CSF) tumor markers or in patients who have less than a PR after induction therapy with negative tumor markers who undergo second-look surgery and are found to have only mature teratoma, residual scar or fibrosis and meet the criteria for CR or PR.

Treatment for germinoma (Stratum 2) will determine, as measured by the 3-year PFS rate, whether simplified chemotherapy prior to dose-reduced radiation therapy is effective for treating children and young adults (ages 3-21 yrs) with localized germinoma who present with serum and CSF hCGβ $\leq$ 50 mIU/ml. PFS and survival distributions of localized germinoma patients who present with serum and/or CSF hCGβ > 50 mIU/ml and $\leq$ 100 mIU/ml will be estimated.

EXPERIMENTAL DESIGN SCHEMA

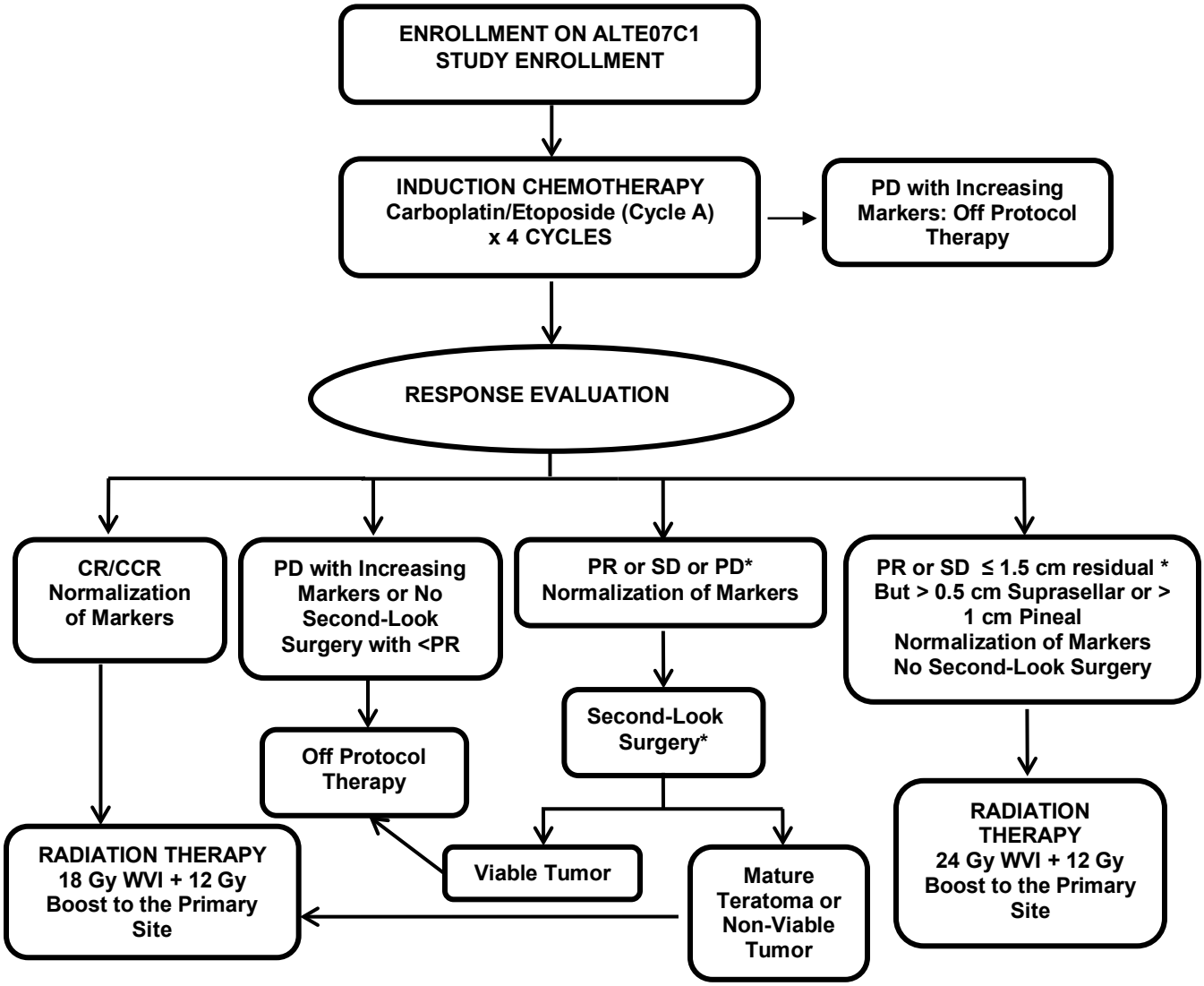
Schema 1: NGGCT Stratum 1



*Second-look surgery is strongly recommended but not required. Patients with increasing mass and normalization of markers should also proceed to second surgery. If a mature teratoma and/or fibrosis are removed, the patient remains on protocol therapy and response should be assessed according to the radiographic response criteria listed in Section 10. If patient has viable tumor after second–look surgery or second-look surgery is not performed and patients do NOT meet criteria for CR or PR, they will be off protocol therapy.
Patients with mature teratoma/scar/fibrosis **only on 2nd look surgery and who fit definitions of CR/PR will be eligible for reduced dose/volume XRT.

CR: Complete response. See Section 10 for specific radiographic and tumor marker definitions of complete response.
PR: Partial response. See Section 10 for specific radiographic and tumor marker definitions of partial response.

Schema 2: Germinoma Stratum 2



CR: **Complete Response**
CCR: **Continued Complete Response**
PR: **Partial Response**
SD: **Stable Disease**
PD: **Progressive Disease**
See Section 10 for specific radiographic and tumor marker definitions of CR, CCR, PR, SD and PD.

* Germinoma patients with PR, SD with > 1.5 cm residual and PD with normalization of hCGβ should be considered for second-look surgery. If histology confirms fibrosis, scar, mature teratoma or non-viable tumor, WVI to 18 Gy followed by local boost of 12 Gy to a total dose of 30 Gy will be delivered. Patients with > 0.5 cm (suprasellar) or > 1 cm (pineal) but ≤ 1.5 cm residual who do not undergo second-look surgery will be treated with WVI to 24 Gy followed by local boost of 12 Gy to a total dose of 36 Gy. If second-look surgery is not performed or patients do not meet criteria for at least PR with ≤ 1.5 cm residual disease or findings following second–look surgery indicate residual viable tumor, patients will be removed from protocol therapy.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Objectives

1.1.1

To determine, as measured by the 3-year progression-free survival (PFS) rate and patterns of failure, whether dose and volume of irradiation can be safely reduced to 30.6 Gy whole ventricular field irradiation (WVI) plus 23.4 Gy primary site boost instead of 36 Gy craniospinal irradiation (CSI) plus primary site boost in the subgroup of children and young adults (ages 3 to ≤ 21 years) with localized non-germinomatous germ cell tumor (NGGCT) who have a magnetic resonance imaging (MRI) and tumor marker criteria (CSF and serum) for confirmed complete response (CR) or partial response (PR) to induction chemotherapy and negative serum and cerebrospinal fluid (CSF) tumor markers OR in patients who have less than a PR after induction chemotherapy with negative tumor markers who undergo a second-look surgery and are found to have only mature teratoma, residual scar or fibrosis and fit the definition of CR/PR after second-look surgery.

1.1.2

To determine, as measured by the 3-year PFS rate and patterns of failure, whether simplified chemotherapy followed by dose-reduced radiation therapy is effective for treating children and young adults (ages 3 to ≤ 21 years) with localized primary central nervous system (CNS) germinoma who present with serum and/or CSF human chorionic gonadotropin-beta (hCGβ) ≤ 50 mIU/ml.

1.1.3

To prospectively evaluate and longitudinally model the cognitive, social, and behavioral functioning of children and young adults who are treated with reduced radiation dose and volume of irradiation in Stratum 1 (NGGCT) and with dose-reduced radiation therapy in Stratum 2 (Germinoma) using the ALTE07C1 protocol. This objective will be assessed independently for the two strata.

1.2 Secondary Objectives

1.2.1

To estimate the PFS and overall survival (OS) distributions of patients with NGGCT treated with 30.6Gy WVI and involved field focal (IFR) boost to 54Gy.

1.2.2

To estimate the PFS and OS distributions of localized germinoma patients who present with **a)** serum and/or CSF hCGβ ≤ 50mIU/ml and **b)** serum and/or CSF hCGβ > 50mIU/ml and ≤ 100mIU/ml.

2.0 BACKGROUND

2.1 Stratum 1: Localized Non-Germinomatous Germ Cell Tumors (NGGCT)

2.1.1 Role of Chemotherapy

Chemotherapy regimens utilizing cisplatin, etoposide and either ifosfamide or cyclophosphamide have greatly improved the outcomes of patients with GCTs over the last few decades. [15-17] In the Second International CNS GCT Study Group Protocol, 16 of 17 assessable patients achieved a CR or PR after two courses of chemotherapy. [18] In a study by Robertson *et al,* 9 of 12 patients demonstrated objective responses to 4 cycles of platinum-based chemotherapy. [19] Carboplatin regimens have shown similar efficacies as compared to cisplatin regimens with the added benefit of easier out-patient administration and less toxicity. [5,19-21] Chemotherapy only strategies, however, despite resulting in high response rates, did not provide an acceptable PFS in NGGCT patients. [20-24] The most recent and completed Children's Oncology Group (COG) ACNS0122 trial for NGGCT patients used a combination of carboplatin/etoposide alternating with ifosfamide/etoposide for a total of 6 induction cycles. Due to the safety and efficacy of this chemotherapy regimen and in an attempt to maintain a relevant comparison group, the current protocol's NGGCT stratum will use the same chemotherapeutic agents as ACNS0122.

2.1.2 Role of Chemoradiotherapy

Radiation therapy (RT) plays an important role in the treatment of NGGCT; however, regimens that use RT alone have only achieved 5-year OS rates of 20%-40%, and most patients relapse within 18 months of diagnosis. [2,25-27] Combined modality therapy including chemotherapy and RT is considered the current standard of care. Since CSI and whole brain irradiation (WBI) are associated with significant late effects, minimizing exposure to RT by stratifying patients according to risk of disease progression after combined modality therapy has been the hallmark of recent international clinical trial designs. [10-12] COG Study ACNS0122 utilized 36 Gy CSI with IFR to 54 Gy following 6 cycles of induction chemotherapy, and this resulted in a 2-year PFS and OS of 84.4 +/- 4% and 93 +/- 3%, respectively. [28-31] In the Société Internationale d'Oncologie Pédiatrique (SIOP) CNS GCT-96 trial (n=172), those patients with localized disease (n=135) received 4 courses of chemotherapy (cisplatin, ifosfamide and etoposide) followed by IFR to 54 Gy. At a median follow-up of 39 months, the reported PFS for the patients with localized disease was 69 $\pm$ 5%. There were 33 relapses in this group including 18 that were local, 3 that were distant and 12 that were combined relapses. This data supports the use of a more localized field of radiation as the failures were predominantly local and distant spinal relapse were quite rare. [32] The Japanese GCT study group treated "intermediate prognosis" patients with 5 cycles of carboplatin and etoposide followed by WVI to 30.6 Gy and IFR to 50 Gy and showed a 10-year PFS and OS rates of 81.5% and 89.3%, respectively. [8,9] Patients with predominantly malignant germ cell tumor elements formed the Japanese "poor prognosis group" and were treated with 3 cycles of ifosfamide, cisplatin, etoposide and CSI. They received an additional 5 cycles of the same chemotherapy after CSI. The 10-year PFS and OS rates were 58.8% and 62.7%, respectively. [8,9]

Given the excellent results reported from the Japanese cooperative group, the SIOP CNS GCT-96 and COG ACNS0122 trial, the combination of induction chemotherapy followed by WVI with IFR to the primary site appears to be a very promising approach for a select group of NGGCT patients.

2.1.3 Rationale for Choosing Patients with CNS NGGCT who achieve a Complete or Partial Response to Induction Chemotherapy as a Subgroup for Reducing Radiation Dose and Volume

The international experience of stratifying CNS NGGCT patients based upon different risk groups such as tumor histology, serum and/or CSF tumor markers (AFP and hCGβ) and responses to neoadjuvant chemotherapy gives insight into what subgroups are most appropriate for reduced radiation. Response to induction chemotherapy has most consistently proven prognostic in previous clinical trials and seems most appropriate for stratification of patients. Of the 34 patients in the SIOP CNS GCT '96 trial with residual disease at the end of radiotherapy, almost half (47%) relapsed and had a much worse PFS (37 ± 10%) compared to those patients in CR post-chemoradiotherapy (86 ± 4%). [33] In the Japanese cooperative group study, for "intermediate-risk" group patients, only 1 of 13 patients relapsed who achieved a CR after receiving between 5 to 8 cycles of chemotherapy compared to 2 out of 10 patients who achieved less than complete response. [8,9]

In the First International Germ Cell Tumor Study, 26 NGGCT patients received four cycles of carboplatin, etoposide and bleomycin. Patients with less than CR received two additional cycles intensified by cyclophosphamide. All 5 patients with less than CR died of disease progression compared to 15 out of 21 (71.4%) patients with CR who were alive without disease at two years from diagnosis. [20] In the Second International CNS Germ Cell Study Group Protocol, 20 NGGCT patients were treated with two to five courses of cisplatin, etoposide, cyclophosphamide and bleomycin. Of the 17 assessable patients for response, 11 achieved CR after two courses and five achieved PR. The median PFS and OS in CR group were 62 and 75 months, respectively, compared to 23 and 41 months in the PR group. [18] Although the complete response rates to chemotherapy in these studies were very promising (65 to 76%), survival data in the PR group were less so, as a result of a chemotherapy only strategy.

The data released documenting the outcomes of patients enrolled on COG ACNS0122 are very promising for patients who achieved a CR (complete radiographic and tumor marker response) and PR (>65% reduction in measurable disease radiographically and normalization of tumor markers) after induction chemotherapy. Of the 104 patients enrolled on ACNS0122, 79 were determined to have localized tumors. Twenty five of 79 patients (31.65%) achieved a CR and 17 of 79 (21.5%) achieved a PR at the end of induction. Of the 18 patients who underwent second-look surgery after induction therapy, 8 were found to have had only a mature teratoma, residual scar or fibrosis on pathology. The median follow-up time for the 64 patients without an event is 3.5 years (range: 73 days to 6 years). Three-year EFS were 92%, 94.1% and 85.7% for these three groups, respectively, without a statistical difference in outcomes among the three groups. Hence, based on these excellent outcomes in these three groups in ACNS0122,

we hypothesize that those patients with a CR or PR to induction chemotherapy (see Section 10 for response definition) and patients whose second-look surgery confirms mature teratoma or scar/fibrosis would be the appropriate group to safely reduce dose and volume of irradiation.

2.1.4 Growing Teratoma Syndrome and Role of Second-Look Surgery

Often times, residual masses post-therapy can be necrosis and fibrosis devoid of tumor or even mature growing teratoma, a phenomenon known as growing teratoma syndrome. [34] It is important to distinguish this entity from residual active or progressive malignancy. On the COG ACNS0122 study, there have been 21 second-look surgeries on 19 patients. The pathology on these surgeries included 13 teratomas (4 growing teratoma syndrome), 4 fibrosis devoid of tumor and 4 NGGCT. [31]

2.2 Stratum 2: Localized Germinoma

Historically, CSI followed by a boost to the primary tumor area has been regarded as the standard treatment for intracranial germinoma. [35-37] However the role of CSI in the treatment of localized germinoma has been called into question due to its late effects and the low incidence of spinal relapses in series that have omitted spinal irradiation. [38-43] These data support the view that it may not be necessary to utilize CSI for patients with non-metastatic germinoma. Excellent responses have been achieved with whole brain irradiation (WBI) or WVI followed by a boost to the primary tumor(s). [41,44,45] Systemic chemotherapy followed by IFR has been tested as a means of reducing radiation doses and/or volume while maintaining high cure rates. [46,47] The finding of relapses within the ventricles (but outside the local radiation field) in multiple studies has induced the SIOP, French Society of Pediatric Oncology (SFOP), and Japanese Brain Tumor clinical trial groups to change from IFR to WVI following chemotherapy for non-metastatic CNS germinoma. [7,48,49]

Local control rates within the irradiated whole ventricular volume remain over 90%. In addition, most relapsing patients are successfully salvaged with chemotherapy and/or RT. [50-53] This encourages exploration of further reduction in CSI and WVI radiation doses in an effort to reduce neurocognitive adverse late effects while maintaining excellent disease control.

A variety of chemotherapy regimens have produced similar response and survival rates. Therefore, the main issue in the management of these patients relates to the short term and long term safety of the chemotherapy used. The use of carboplatin in extracranial NGGCTs has raised concerns, following the results of two randomized studies that demonstrated the superiority of *cisplatin over carboplatin.* However, in CNS germinoma, carboplatin regimens have shown similar efficacy when compared with cisplatin regimens. [20,54] An institutional review of patients treated either with cisplatin and/or ifosfamide based chemotherapy revealed major risks for patients suffering from diabetes insipidus (DI). Despite vigilant monitoring of electrolytes and hormone (DDAVP) substitution adjustments significant variations in sodium levels and unexpected episodes of hyponatremia with consecutive complications and prolongation of hospital admissions were documented. [55,56] Therefore an ifosfamide-sparing regimen as successfully documented by the Japanese GCT study group.[7,57] and Children's Hospital Los Angeles experience should be adopted. [58-60] These data strongly suggest

that chemotherapy in germinoma can be safely simplified using a combination of carboplatin and etoposide with the advantage of easier out-patient administration when appropriate and reduced risk of hyperhydration-associated metabolic complications while still maintaining high cure rates with a potentially lower risk of late effects.

2.2.1 Human Chorionic Gonadotropin (hCG & hCGβ) and Need for Tissue Diagnosis

There are conflicting data regarding the maximum level of hCGβ in germinoma and its prognostic significance. Sawamura et al reported that 14 of 74 germinoma patients had elevated hCG serum levels between 5-200 mIU/ml. The 10-year OS for patients with germinoma with normal serum hCG was 90%, which was significantly higher than the 60% for patients with hCGβ-secreting germinomas. [61] However, in a retrospective review of germinoma patients with (n=39) and without (n=131) hCGβ elevation, no statistical difference in response to chemotherapy, clinical outcome or rate of recurrence was found. [62] This finding is supported by other studies, underscoring the fact that elevated hCGβ does not affect outcome. [40,63] The Japanese GCT Study Group used an intensified protocol for patients with germinoma and hCGβ secretion with higher doses of radiation therapy and 5 courses of post-irradiation chemotherapy. In an interim report of the current Japanese protocol, Matsutani et al reported no statistical difference in serum hCG or hCGβ between recurrent and non-recurrent patients. Following these results the Japanese CNS-GCT study group currently treats all localized germinoma patients (regardless of the level of hCGβ secretion) with the same regimen consisting of 3 cycles of carboplatin and etoposide followed by WVI at a dose of 24 Gy.[7]

Based on these data and intensive review within the CNS study committee, the present study's Stratum 2 (Germinoma) will include patients with elevations of serum or CSF hCGβ levels up to 100 mIU/ml provided AFP levels are in the normal range.

2.2.2 Subclinical Ventricular Metastases and Bifocal Germinoma

Chemotherapy serves two roles defined by the irradiated volume: chemotherapy may eradicate neuraxis and extra-CNS metastatic disease outside of the volume of irradiation and it may reduce the tumor burden or increase the sensitivity of tumor cells to irradiation within the irradiated volume. The burden of metastatic disease that may be eradicated using chemotherapy and volume of residual tumor or magnitude of the response to chemotherapy that allows lower doses of irradiation to be utilized are unknown. That ventricular irradiation is critical to the success of combined modality regimens suggests that subclinical ventricular metastatic disease is present at the time of diagnosis in a significant proportion of patients and that current chemotherapy regimens are inadequate to eradicate this subclinical disease. In keeping with past protocols and series that have obtained excellent results, metastatic disease will be defined as neuroimaging evidence of intracranial or spinal metastatic disease or CSF involvement based on cytological evaluation of fluid obtained from a lumbar puncture. Therefore, intraoperative or endoscopic observed studding of ventricles alone (without evidence of seeding on MRI or CSF) will **NOT** be used to classify patients as having metastatic disease. Similarly, patients with bifocal lesions (pineal and suprasellar lesions) fare as well as those with unifocal lesions when treated with chemotherapy and ventricular irradiation. [49,64,65] These patients will be eligible

for study participation and, in accordance with the SFOP and SIOP approach, a biopsy will **NOT** be required if the clinical presentation (evidence of DI in particular) and imaging characteristics are typical in patients who present with serum and CSF hCGβ ≤ 50mIU/ml. Germinoma located within a ventricle with unifocal parenchymal extension will also be treated as localized germinoma.

2.2.3 Neurocognitive Outcomes and QOL

The late effects of CSI have long been recognized, particularly in children. Long term sequelae include auditory and visual impairment, endocrine and neurocognitive dysfunction and secondary malignancies. [10-14] Neurocognitive sequelae associated with CSI has garnered increased attention in the past two decades, with the resulting research consistently demonstrating treatment-related deficits in core neurocognitive processes such as attention, working memory, executive functioning, and processing speed. [68,69] These deficits interfere with age-appropriate acquisition of knowledge so that overtime declines may emerge in IQ and academic achievement scores. [70-71] Additionally, neurocognitive late effects are often accompanied with impairments in social and behavioral functioning, and may adversely impact functional capacity well into adulthood. [72-74] A retrospective study evaluating long-term QOL in 52 germinoma survivors into adulthood identified significant problems: only 6 of 44 patients were married, 21 patients had no occupation and 7 of 11 formerly employed patients had left their jobs.[66]

The literature on neurocognitive and quality of life outcomes specifically among survivors of CNS Germ Cell tumors is limited, and the findings to date are based on reports with small sample size and/or retrospective methodology. The majority of these reports indicate at least some degree of cognitive impairment. [75-77] More recently, O'Neil et al [78] reported preservation of neurocognitive, social, and emotional functioning in their sample of 20 pediatric CNS Germinoma patients treated with chemotherapy and reduced dose ventricular field irradiation. Their results did, however, show trends towards lowered performance in processing speed scores, and the continued overall preservation remains to be seen with longer follow up time. There clearly is a need to assemble psychometrically sound data in a sufficiently large sample using a prospective design framework to document longitudinal trends in these outcomes.

Since September 2008, a standardized battery of age-appropriate cognitive, social, emotional, and behavioral tests is provided by the open COG protocol ALTE07C1. The ACNS1123 study will enroll patients onto ALTE07C1 to evaluate cognitive, social, emotional and behavioral functioning post-diagnosis. The current study will be the first prospective study evaluating neurocognitive function longitudinally in a homogenously treated cohort of patients with CNS GCT. The resulting longitudinal models will describe changes in neurocognitive function. These models will also provide the means of exploring associations of covariates such as tumor location, age and the dose/volume of irradiation with outcomes.

3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the COG Registry system once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help.

In order for an institution to maintain COG membership requirements, every newly diagnosed patient needs to be offered participation in ACCRN07, *Protocol for the Enrollment on the Official COG Registry, The Childhood Cancer Research Network (CCRN)*.

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. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

Please see Appendix I for detailed CTEP Registration Procedures for Investigators and Associates, and CTSU Registration Procedures including: how to download site registration documents; requirements for site registration, submission of regulatory documents and how to check your site's registration status.

3.1.2 IRB Approval

Sites must obtain IRB/REB approval for this protocol and submit IRB/REB approval and supporting documentation to the Cancer Trials Support Unit (CTSU) Regulatory Office before they can be approved to enroll patients. Allow 3 business days for processing. The submission must include a fax coversheet (or optional CTSU IRB Transmittal Sheet) and the IRB approval document(s). The CTSU IRB Certification Form may be submitted in lieu of the signed IRB approval letter. All CTSU forms can be located on the CTSU web page (https://www.ctsu.org). Any other regulatory documents needed for access to the study enrollment screens will be listed for the study on the CTSU Member's Website under the RSS Tab.

IRB/REB approval documents may be faxed (1-215-569-0206),
E-mailed (CTSURegulatory@ctsu.coccg.org) or mailed to the CTSU Regulatory office.

When a site has a pending patient enrollment within the next 24 hours, this is considered a "Time of Need" registration. For Time of Need registrations, in addition to marking your submissions as 'URGENT' and faxing the regulatory documents, call the CTSU Regulatory Helpdesk at: 1-866-651-CTSU. For general (non-regulatory) questions call the CTSU General Helpdesk at: 1-888-823-5923.

Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' web site by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

3.1.3 Study Enrollment

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the lead protocol organization (LPO) or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN, site staff and the results from the rapid central pathology screening review have confirmed the patient is eligible.

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL (https://open.ctsu.org). For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

3.1.4 Timing

Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than five **(5)** calendar days after the date of study enrollment. **Patients who are started on protocol therapy on a Phase II study prior to study enrollment will be considered ineligible**.

Timing for enrollment will begin after the last definitive surgical intervention or clinical diagnosis. See Section 3.2.5.

All clinical and laboratory studies to determine eligibility must be performed within 14 days prior to enrollment unless otherwise indicated in the eligibility section below.

3.2 Patient Eligibility Criteria

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.

All clinical and laboratory studies to determine eligibility must be performed within 14 days prior to enrollment. Laboratory values need not be repeated if therapy starts within 14 days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are >14 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies must be obtained as outlined in Section 3.2.3 .

See Section 7.1 for required studies to be obtained prior to starting protocol therapy.

INCLUSION CRITERIA

3.2.1 Age

Patients must be ≥ 3 years and ≤ 21 years at the time of study enrollment.

3.2.2 Diagnosis

Patients must be newly diagnosed with localized primary CNS NGGCT (Stratum 1) or localized primary CNS germinoma (Stratum 2). Germ cell tumors located in the suprasellar, pineal, bifocal (pineal + suprasellar) and ventricles are eligible. Tumors present in the above mentioned locations and with unifocal parenchymal extension are eligible. Please see exclusion criteria in Section 3.2.6.

- Stratum 1(NGGCT): Patients must have one of the following criteria.
  - Patients with serum and/or CSF hCGβ > 100 mIU/mL or any elevation of serum and/or CSF AFP > 10 ng/mL or greater than

the institutional normal are eligible, irrespective of biopsy results.

- Patients with any of the following elements on biopsy/resection are eligible, irrespective of serum and/or CSF hCGβ and AFP levels: endodermal sinus tumor (yolk sac), embryonal carcinoma, choriocarcinoma, malignant/immature teratoma and mixed GCT with malignant GCT elements

- Stratum 2 (Germinoma):
  Patients must have both serum and CSF markers obtained (unless obtaining CSF is medically contraindicated) and must have one of the following criteria to be eligible.

  - Patients with institutional normal AFP (or ≤ 10 ng/mL if no institutional normal exists) in both serum and CSF (unless medically contraindicated) AND hCGβ 5 - ≤ 50 mIU/ml in serum and/or CSF (unless medically contraindicated) (only 1 is required to be elevated) are eligible.. No histologic confirmation required.

  - Patients with bifocal (pineal + suprasellar) involvement or pineal lesion with diabetes insipidus (DI) AND hCGβ ≤ 100 mIU/ml in serum and/or CSF AND institutional normal AFP (or ≤ 10 ng/mL if no institutional normal exists) in both serum and CSF (unless medically contraindicated) are eligible. No histologic confirmation required.

  - Patients with histologically confirmed germinoma or germinoma mixed with mature teratoma and hCGβ ≤ 100 mIU/ml in serum and/or CSF and institutional normal AFP (or ≤ 10 ng/mL if no institutional normal exists) in both serum and CSF (unless medically contraindicated) are eligible..

Note: Patients who had more than one surgery/biopsy are eligible.

3.2.3 Imaging

Imaging studies must be obtained within 2 weeks prior to study enrollment.

Cranial MRI
All patients must have a cranial MRI with and without gadolinium at diagnosis/prior to enrollment. If surgical resection is performed, patients must have pre-operative and post-operative cranial MRI with and without gadolinium. The post-operative brain MRI should be obtained within 72 hours of surgery. If patient has a biopsy only, post-operative cranial MRI is recommended but not required.

Spinal MRI
All patients must have a spine MRI with gadolinium obtained at diagnosis/prior to enrollment.

Note: If the spine study is performed for the first time after surgical resection or biopsy, it is recommended to be obtained with and without gadolinium.

3.2.4 CSF

3.2.4.1 CSF Cytology

Lumbar CSF must be obtained prior to study enrollment unless medically contraindicated. If a patient undergoes surgery and lumbar CSF cannot be obtained at this time, then it should be performed at least 10 days following surgery before study enrollment. False positive cytology can occur within 10 days of surgery.

Note: Patients with positive CSF cytology obtained prior to 10 days after surgery may have cytology repeated to determine eligibility.

3.2.4.2 CSF Tumor Markers

Patients must have CSF tumor markers obtained prior to enrollment unless medically contraindicated. Ventricular CSF obtained at the time of CSF diversion procedure (if performed) is acceptable for tumor markers but lumbar CSF is preferred. In case CSF diversion and biopsy/surgery are combined, CSF tumor markers should be collected first.

3.2.5 Timing

Patients must be enrolled on ALTE07C1 prior to enrollment on ACNS1123.

Patients must be enrolled within 31 days of definitive diagnostic surgery (Day 0) or clinical diagnosis.

3.2.6 Organ Function Requirements

3.2.6.1 Adequate Bone Marrow Function Defined As:

- Peripheral absolute neutrophil count (ANC) ≥ 1,000/μL
- Platelet count ≥ 100,000/μL (transfusion independent)
- Hemoglobin ≥ 8.0 g/dL (may receive RBC transfusions)

3.2.6.2 Adequate Renal Function Defined As:

- Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m^2 or
- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

3.2.6.3 Adequate Liver Function Defined As:

- Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and
- SGOT (AST) and SGPT (ALT) < 2.5 x upper limit of normal (ULN) for age.

3.2.6.4 Central Nervous System Function Defined As:

- Patients with seizure disorder may be enrolled if well controlled.
- Patients must not be in status, coma or assisted ventilation prior to study enrollment.

EXCLUSION CRITERIA

3.2.7 Mature Teratoma
Patients with mature teratoma or completely resected immature teratoma with normal tumor markers are not eligible.

3.2.8 Tumors Outside Ventricles
Patients with tumors located outside the ventricles (basal ganglia, thalamus) are not eligible.

3.2.9 Metastatic Disease
Patients with metastatic disease by cranial or spinal MRI evaluation or CSF cytology (unless medically contraindicated) are not eligible.

3.2.10 Prior Therapy
Patients must not have received any prior tumor-directed therapy other than surgical intervention and corticosteroids.

3.2.11 Pregnancy and Breast Feeding

3.2.11.1
Female patients who are pregnant are ineligible.

3.2.11.2
Lactating females are not eligible unless they have agreed not to breastfeed their infants.

3.2.11.3
Female patients of childbearing potential are not eligible unless a negative pregnancy test result has been obtained.

3.2.11.4
Sexually active patients of reproductive potential are not eligible unless they have agreed to use an effective contraceptive method for the duration of their study participation.

REGULATORY

3.2.12
All patients and/or their parents or legal guardians must sign a written informed consent.

3.2.13
All institutional, FDA, and NCI requirements for human studies must be met.

4.0 TREATMENT PROGRAM

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

4.1 Overview of Treatment Plan

Induction Chemotherapy
All patients must begin therapy within 31 days of definitive diagnostic surgery or clinical diagnosis and 5 calendar days from enrollment on study. Each subsequent cycle of Induction chemotherapy will begin when ANC > 1,000/μL and platelets > 100,000/μL and when off filgrastim (G-CSF) for at least 48 hours (if applicable).

Cycle A: (21 Days)
Carboplatin (600 mg/m^2/dose) Day 1
Etoposide (150 mg/m^2/dose) Days 1-3

Cycle B: (21 Days)
Ifosfamide (1800 mg/m^2/dose) Days 1-5
Etoposide (100 mg/m^2/dose) Days 1-5
Mesna (1800mg/m^2/day) Days 1-5
Filgrastim (G-CSF) (5 micrograms/kg/day) Days 6-15 or until ANC > 1500/μL

Growing Teratoma Syndrome
Second-look surgery is strongly recommended in patients with normalization of markers who fail to achieve a radiographic CR or PR to induction chemotherapy and in patients with increasing size of the mass on MRI scan and negative markers at any time during Induction chemotherapy. If a mature teratoma and/or fibrosis are removed, the patient remains on protocol and should continue therapy as planned. Response should be assessed according to the radiographic and tumor marker response criteria listed in Section 10.

Chemotherapy for NGGCT (Stratum 1)

Week									
0	3	**Evaluation**	6	9	**Evaluation**	12	15	**Response Evaluation**
Cycle A	Cycle B	**(MRI/tumor markers)**	Cycle A	Cycle B	**(MRI/tumor markers)**	Cycle A	Cycle B	**(MRI/tumor markers)**

Patients will receive 6 cycles of induction chemotherapy consisting of carboplatin and etoposide (Cycles 1, 3, and 5) alternating with ifosfamide and etoposide (Cycles 2, 4, and 6). The entire length of Induction is approximately 18 weeks unless delay occurs due to myelosuppression or unanticipated toxicity.

Following induction chemotherapy, those patients in CR or PR will undergo radiation therapy 30.6 Gy WVI with IFR boost to 54 Gy in 1.8 Gy daily fractions.

For those patients with PR, SD or PD and normalization of tumor marker levels in serum and CSF, second- look surgery is strongly recommended. Patients who achieve CR/PR via second-look surgery (and have histology consistent with fibrosis, scar or mature teratoma) will then proceed to radiation therapy as above.

Patients with positive markers or who have < PR after induction chemotherapy/second-look surgery will be removed from protocol therapy.

Patients with residual viable malignant elements (except mature teratoma) on second-look surgery will be removed from protocol therapy.

Patients who are unable to undergo a second-look surgery due to safety or other reasons, will be taken off protocol therapy if they do not meet criteria for PR/CR (imaging and tumor markers).

Chemotherapy for Germinoma (Stratum 2)

Week					
0	3	**Evaluation**	6	9	**Response Evaluation**
Cycle A	Cycle A	**(MRI/tumor markers)**	Cycle A	Cycle A	**(MRI/tumor markers)**

Patients will receive 4 cycles of Induction chemotherapy consisting of carboplatin and etoposide. The entire length of Induction is 12 weeks unless delay occurs due to myelosuppression or unanticipated toxicity.

Following Induction those patients in CR/CCR will undergo radiation therapy (see guidelines below).

Patients with PR, SD with > 1.5 cm residual and PD with normalization of hCGβ should be considered for second-look surgery after completion of chemotherapy. Patients with evidence of new lesion(s) and/or increase in tumor markers will be removed from protocol therapy.

- If findings following (second-look) surgery are consistent with fibrosis, scar, mature teratoma or non-viable tumor, patients will receive 18 Gy WVI followed by 12 Gy boost to the primary site in 1.5 Gy daily fractions.

- If findings following (second-look) surgery indicate residual viable malignant elements, patients will be removed from protocol therapy.

Patients who have SD or PR with > 0.5 cm (suprasellar) or > 1 cm (pineal) but ≤ 1.5 cm residual disease and do not undergo a second-look surgery due to safety or other reasons, will receive 24 Gy WVI followed by 12 Gy boost to the primary site in 1.5 Gy daily fractions.

- Patients who have SD or PR with greater than 1.5 cm residual tumor or PD but are unable to undergo a second-look surgery due to safety or other reasons, will be taken off protocol.

Radiation Therapy for NGGCT (Stratum 1)
Radiation therapy will be administered to all volumes in fractions of 1.8 Gy given once daily. See Section 10.0 for response definitions.

a. CR and PR: WVI to 30.6 Gy followed by IFR boost of 23.4 Gy to a total dose of 54 Gy.

b. Stable disease (SD) or progressive disease (PD): Off protocol therapy unless a second-look surgery renders the patient in CR or PR.

Radiation Therapy for Germinoma (Stratum 2)
Radiation will be administered to all volumes in fractions of 1.5 Gy given once daily. See Section 10.0 for response definitions.

a. CR and continuous complete response (CCR): WVI to 18 Gy followed by local boost of 12 Gy to a total dose of 30 Gy.

b. PR, SD and PD with normal markers: If (Second-look) surgery is consistent with no viable tumor or mature teratoma, WVI to 18 Gy followed by IFR boost of 12 Gy to a total dose of 30 Gy will be delivered. If any viable tumor (including Germinoma) is found, patients will come off protocol therapy.

c. PR or SD with normal markers: Patients with > 0.5 cm suprasellar or > 1 cm pineal but ≤ 1.5 cm residual who do not undergo second-look surgery will be treated with WVI to 24 Gy followed by local boost of 12 Gy to a total dose of 36 Gy. If second-look surgery is not performed and patients do not meet criteria for at least PR with ≤ 1.5 cm residual disease, patients will be off protocol therapy.

d. Progressive disease (PD): Patients with PD with normal serum and CSF markers after 4 cycles of chemotherapy will proceed to (second-look) surgery. If (second-look) surgery findings are consistent with mature teratoma or non-viable tumor, WVI to 18 Gy followed by IFR boost of 12 Gy to a total dose of 30 Gy will be delivered. Patients with any viable tumor (except mature teratoma) will be off protocol therapy. Patients with evidence of new lesion(s) and increasing markers or patients who do not have second-look surgery will be removed from protocol therapy.

4.2 Concomitant Therapy Restrictions

4.2.1

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary. Antiemetics may be used per institutional guidelines. The routine use of steroids as an antiemetic is discouraged.

4.2.2 Diabetes Insipidus (DI)

Patients with DI should have monitoring of endocrine function and consultation with an endocrinologist is strongly recommended for guidance during fluid and chemotherapy administration.

For COG Supportive Care Guidelines see:
https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

4.3 Stratum 1 (NGGCT) Administration Guidelines for Induction

4.3.1 Cycle A (Cycles 1, 3, 5)

CARBOplatin: IV over 15-60 minutes
Day: 1
Dose: 600 mg/m^2/dose

Avoid use of aluminum containing needles or administration sets.

Medication errors have occurred due to confusion between CISplatin (Platinol®) and CARBOplatin (PARAplatin®).

Etoposide: IV over 60-120 minutes
Days: 1-3
Dose: 150 mg/m^2/dose

Infuse diluted solution (concentration $\leq$ 0.4 mg/mL) over at least 60-120 minutes; slow rate of administration if hypotension occurs. Rate should not exceed 300 mg/m^2/hour (10 mg/kg/hour) (hypotension risk). The use of an in-line filter during the infusion is suggested.

Special precautions: Etoposide can be mixed in 0.9% NaCl or D_5W. Avoid use of large volumes of D_5W due to potential development of hyponatremia.

Stability: Leaching of diethylhexyl phthalate (DEHP) from PVC bags occurred with etoposide 0.4 mg/mL in 0.9% NaCl solution. To avoid leaching, prepare the etoposide solution as close as possible, preferably within 4 hours, to the time of administration or alternatively as per institutional policy. Glass or polyethylene-lined (non-PVC) containers and polyethylene-lined tubing may be used.

See the Parenteral Chemotherapy Administration Guidelines (CAG) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Section 5.0 for Dose Modifications based on Toxicities.

The therapy delivery map (TDM) for Cycle A of Induction is on the next page.

Each cycle of Induction will begin when ANC > 1,000/μL and platelets > 100,000/μL and when off filgrastim (G-CSF) for at least 48 hours.

4.3.2 Stratum 1 NGGCT Cycle A Induction Induction consists of six cycles (Cycle A and Cycle B). Cycle A is given during Cycles 1, 3 and 5. This Cycle lasts 3 weeks (21 days).	_____ Patient name or initials _____ DOB

Criteria to start this cycle: ANC > 1,000/μL and platelets > 100,000/μL and off filgrastim (G-CSF) for at least 48 hours. Extensive details are in Section 4.0 (treatment overview). This cycle lasts 21 days and the TDM for this cycle is on **1** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
CARBOplatin (CARBO)	IV over 15-60 minutes	600 mg/m^2/dose	1	See Section 5.1.1 if renal function is abnormal.	a. History, PE (Ht, Wt, VS) with Neurologic Exam, Performance Status b. CBC (differential, platelets) c. Urinalysis d. Electrolytes (including BUN, Calcium, PO_4, Magnesium, Sodium, Potassium) e. Total protein, AST, ALT, albumin, bilirubin **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Etoposide (ETOP)	IV over 60-120 minutes	150 mg/m^2 dose	1-3	See admin guidelines in Section 4.3.1	

Enter Cycle #: _____ Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	CARBO ____mg	ETOP ____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below			
		1	____mg	____mg	a, b, c, d, e	
		2		____mg		
		3		____mg		
		4				
		8			b, d@	
		15			b, d@	
		22	Start Cycle B on Day 22 or when blood count parameters are met (whichever occurs later).			

@ Obtain weekly if clinically indicated.

See Section 5.0 for Dose Modifications for Toxicities and the COG website posted materials for Supportive Care Guidelines.

4.3.3 Cycle B (Cycles 2, 4, 6)

Ifosfamide: IV over 60 minutes
Days: 1-5
Dose: 1800 mg/m^2/dose

Suggested hydration: Administer 3,000 mL/m²/day (125 mL/m²/hour) using fluid containing D_5W/0.45% NaCl or 0.9% NaCl. Achieve urine specific gravity ≤ 1.010 prior to start of ifosfamide. Monitor for adequate urine output as per institution guidelines. May use diuretics (eg, furosemide) to increase urine output. Consider adding potassium and magnesium to prevent electrolyte deficiencies.

Etoposide: IV over 60-120 minutes*
Days: 1-5
Dose: 100 mg/m^2/dose

Note: Infuse as diluted solution (concentration ≤ 0.4 mg/mL); *slow rate of administration if hypotension occurs. Rate should not exceed 300 mg/m^2/hour (10 mg/kg/hour) (hypotension risk). The use of an in-line filter during the infusion is suggested.

Special precautions: Etoposide can be mixed in 0.9% NaCl or D_5W. Avoid use of large volumes of D_5W due to potential development of hyponatremia.

Mesna: IV (short or continuous infusion)
Days: 1-5
Total Dose: 1800 mg/m^2/day

IV short or continuous infusion: For prophylaxis of hemorrhagic cystitis, the total daily mesna dose is equal to 100% of the daily ifosfamide dose. Mesna can be administered in 5 divided doses by **short intravenous infusion** over 15 to 30 minutes. The initial bolus dose of mesna may be administered 15 minutes before or at the same time as the ifosfamide dose; subsequent doses are given 3, 6, 9, and 12 hours after the start of ifosfamide.

For example: if the ifosfamide dose is 1000 mg, then the total daily mesna dose is 1000 mg; 200 mg of mesna will be given 15 minutes before or with the ifosfamide dose (Hour 0) and 4 boluses of 200 mg each will be given at Hours 3, 6, 9 and 12.

This total daily dose of mesna can also be administered as IV **continuous infusion**. The continuous infusion should be started 15-30 minutes before or at the same time as ifosfamide and finished no sooner than 12 hours after the end of the ifosfamide infusion.

For example: if the ifosfamide dose is 1000 mg, then the total daily mesna dose is 1000 mg; the 1000 mg mesna continuous infusion will start 15-30 minutes before or at the same time as the ifosfamide and be completed no sooner than 12 hours after **the end** of the ifosfamide infusion. If ifosfamide is administered over 2 hour and mesna is started 30 minutes before the ifosfamide infusion, the total mesna infusion will last at least 14 hours and 30 minutes.

Use of oral mesna:
The oral dose of mesna is **twice** the IV dose. Patients able to tolerate oral mesna may receive the last **FOUR** bolus doses (originally at Hours 3, 6, 9, and 12) orally at 40% of the ifosfamide dose. The oral doses will be administered at Hours 1, 4, 7, and 10.

For example: if the ifosfamide dose is 1000 mg, then the first 200 mg dose of mesna will be given IV 15 minutes before or with the ifosfamide dose (Hour 0) and **FOUR** oral doses of 400 mg each will be given at Hours 1, 4, 7, and 10.

Administer tablets or diluted parenteral solution. To decrease sulfur odor, dilute mesna parental solution before oral administration. The solution can be diluted 1:1 to 1:10 in water, carbonated cola drinks, fruit juices (grape, apple, tomato and orange) or plain or chocolate milk. The most palatable is chilled grape juice. Tablets are 400 mg each and can be divided into 200 mg/0.5 tabs so dosing can be rounded up to nearest 200mg. Administer doses on a schedule as determined by timing of ifosfamide administration. If a dose is missed, administer dose immediately. Give the next scheduled dose according to the original dosing schedule. Do not deviate from the original schedule. Notify provider if a dose is delayed or missed. If a dose is vomited within 2 hours of administration, repeat the dose orally or switch to intravenous mesna.

Filgrastim: Subcutaneous (preferred) or IV
Days: Daily, starting on Day 6 and continue for 10 days until ANC > 1500/μL after the expected nadir.
Dose: 5 mcg/kg/dose.

Note: The use of filgrastim is strongly recommended, however, patients receiving PEG-filgrastim will not be excluded.

See the Parenteral Chemotherapy Administration Guidelines (CAG) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Section 5.0 for Dose Modifications based on Toxicities.

The therapy delivery map (TDMs) for Cycle B of Induction is on the next page.

Each cycle of Induction will begin when ANC > 1,000/μL and platelets > 100,000/μL and when off of filgrastim (G-CSF) for at least 48 hours.

4.3.4 Stratum 1 NGGCT Cycle B Induction Induction consists of six cycles (Cycle A and Cycle B). Cycle B is given during Cycles 2, 4 and 6. This Cycle lasts 3 weeks (21 days).	_____ Patient name or initials _____ DOB

Criteria to start this cycle: ANC > 1,000/µL and platelets > 100,000/µL and off filgrastim (G-CSF) for at least 48 hours. Extensive details are in Section 4.0 (treatment overview). This cycle lasts 21 days and the TDM for this cycle is on **1** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Ifosfamide (IFOS)	IV over 60 minutes	1800 mg/m^2/dose	1-5	See admin guidelines in Section 4.3.3	a. History, PE (Ht, Wt, VS) with Neurologic Exam, Performance Status b. CBC (differential, platelets) c. Urinalysis d. Electrolytes (including BUN, Calcium, PO_4, Magnesium, Sodium, Potassium) e. Serum Creatinine, CrCl or GFR f. Total protein, AST, ALT, albumin, bilirubin g. Lumbar CSF cytology* h. Lumbar CSF Markers (hCG, AFP)* i. Serum Markers (hCG, AFP) j. Brain MRI with and without gadolinium k. Spine MRI with and without gadolinium l. Audiogram or BAER m. Endocrine function * Lumbar CSF should be obtained unless medically contraindicated. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Etoposide (ETOP)	IV over 60-120 minutes	100 mg/m^2/dose	1-5	See admin guidelines in Section 4.3.3	
Mesna (MESNA)	IV (short or continuous infusion)	See Section 4.3.3	1-5	Administer concurrently with ifosfamide	
Filgrastim (G-CSF)	SubQ (preferred) or IV	5 mcg/kg/dose	Daily on Days 6-15	Start G-CSF on Day 6 and continue for ten days or until ANC > 1500/µL.	

Enter Cycle #: _____ Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	IFOS ____mg	ETOP ____mg	MESNA__mg	G-CSF ____mcg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below					
		1	____mg	____mg	____mg		a, b, c, d, e, f	
		2	____mg	____mg	____mg			
		3	____mg	____mg	____mg			
		4	____mg	____mg	____mg			
		5	____mg	____mg	____mg			
		6				____mg		
		8					b, d@	
		15					b, d@	
		21					I$, j$ [a,b,c,d,e,f,g, h,i,j,k,l,m]#	Indicate date of last G-CSF dose _____
		22	Start Cycle A on Day 22 or when blood count parameters are met (whichever occurs later). Upon completion of Induction, patients will undergo response evaluation.					

$ Obtain after cycles 2 and 4 @ Obtain weekly if clinically indicated.

Obtain at completion of Induction (after Cycle 6).

See Section 5.0 for Dose Modifications for Toxicities and the COG website posted materials for Supportive Care Guidelines.

4.4 Stratum 2 (Germinoma) Administration Guidelines for Induction

4.4.1 Cycle A (Cycles 1-4)

CARBOplatin: IV over 15-60 minutes
Day: 1
Dose: 600 mg/m^2/dose

IV: Infuse the diluted solution over 15-60 minutes. Avoid use of aluminum containing needles or administration sets.

Medication errors have occurred due to confusion between CISplatin (Platinol®) and CARBOplatin (PARAplatin®).

Etoposide: IV over 60-120 minutes
Days: 1-3
Dose: 150 mg/m^2/dose

Infuse diluted solution (concentration $\leq$ 0.4 mg/mL) over at least 60-120 minutes; slow rate of administration if hypotension occurs. Rate should not exceed 300 mg/m^2/hour (10 mg/kg/hour) (hypotension risk). The use of an in-line filter during the infusion is suggested.

Special precautions: Etoposide can be mixed in 0.9% NaCl or D_5W. Avoid use of large volumes of D_5W due to potential development of hyponatremia.

Stability: Leaching of diethylhexyl phthalate (DEHP) from PVC bags occurred with etoposide 0.4 mg/mL in 0.9% NaCl solution. To avoid leaching, prepare the etoposide solution as close as possible, preferably within 4 hours, to the time of administration or alternatively as per institutional policy. Glass or polyethylene-lined (non-PVC) containers and polyethylene-lined tubing may be used.

See the Parenteral Chemotherapy Administration Guidelines (CAG) on the COG website at: https://members.childrensoncologygroup.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAGs for suggestions on hydration, or hydrate according to institutional guidelines.

See Section 5.0 for Dose Modifications based on Toxicities.

The therapy delivery map (TDM) for Cycle A of Induction is on the next page.

Each cycle of Induction will begin when ANC > 1,000/µL and platelets > 100,000/µL and when off filgrastim (G-CSF) for at least 48 hours.

4.4.2 Stratum 2 Germinoma Cycle A Induction Induction consists of four cycles. Cycle A is given in all four cycles. This Cycle lasts 3 weeks (21 days).	_____ Patient name or initials _____ DOB

Criteria to start this cycle: ANC > 1,000/µL and platelets > 100,000/µL and off filgrastim (G-CSF) for at least 48 hours. Extensive details are in Section 4.0 (treatment overview). This cycle lasts 21 days and the TDM for this cycle is on **1** page.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
CARBOplatin (CARBO)	IV over 15-60 minutes	600 mg/m^2/dose	1	See Section 5.1.1 if renal function is abnormal.	a. History, PE (Ht, Wt, VS) with Neurologic Exam, Performance Status b. CBC (differential, platelets) c. Urinalysis d. Electrolytes (including BUN, Calcium, PO_4, Magnesium, Sodium, Potassium) e. Serum Creatinine, CrCl or GFR f. Total protein, AST, ALT, albumin, bilirubin g. Lumbar CSF cytology* h. Lumbar CSF Markers (hCG, AFP)* i. Serum Markers (hCG, AFP) j. Brain MRI with and without gadolinium k. Spine MRI with and without gadolinium l. Audiogram or BAER m. Endocrine function * Lumbar CSF should be obtained unless medically contraindicated. **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Etoposide (ETOP)	IV over 60-120 minutes	150 mg/m^2/dose	1-3	See admin guidelines in Section 4.4.1	

Enter Cycle #: _____ Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	CARBO ____mg	ETOP ____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below			
		1	____mg	____mg	a, b, c, d, f	
		2		____mg		
		3		____mg		
		4				
		8			b, d@	
		15			b, d@	
		21			i$, j$ [a,b,c,d,e,f,g,h,i,j,k,l,m]#	
		22	Start next cycle on Day 22 or when blood count parameters are met (whichever occurs later). Upon completion of Induction, patients will undergo response evaluation.			

$ Obtain after Cycle 2. @ Obtain weekly if clinically indicated

Obtain at completion of Induction (after Cycle 4).

See Section 5.0 for Dose Modifications for Toxicities and the COG website posted materials for Supportive Care Guidelines.

5.0 DOSE MODIFICATIONS FOR TOXICITIES

5.1 Carboplatin

5.1.1 Nephrotoxicity

Patients who have compromised renal function should undergo a GFR (see table in Section 3.2.6.2). If the corrected GFR is <100 mL/min/1.73m^2, the carboplatin dose should be calculated per the modified Calvert Formula using a target AUC of 5. **Please note that the equation below calculates the ACTUAL mg of carboplatin to be given and NOT the dose per surface area. Also note that the maximum dose calculated using the modified Calvert Formula must not exceed the originally planned dose of 600 mg/m^2. Each final total daily dose of carboplatin should be checked to ensure that it does not exceed this amount.**

Modified Calvert Formula:

$$\text{Carboplatin Total Dose in mg/day} = \left\{\frac{\text{(Corrected GFR x surface area)}}{1.73} + (15 \times \text{surface area})\right\} \times \text{AUC}$$

Alternately, the equation may also be expressed as follows:

$$\text{Carboplatin Total Dose in mg/day} = \{\text{(Uncorrected GFR)} + (15 \times \text{surface area})\} \times \text{AUC}$$

Example Carboplatin dosage calculation:

Example 1:

Surface area = 0.5m^2 Corrected GFR = 70mL/min/1.73m^2

$$\text{Total dose in mg/day} = \left\{\frac{70 \times 0.5}{1.73} + 15(0.5)\right\} \times 5$$

Dose = (20.23 + 7.5) x 5 = 139 mg/day

Double check dose to ensure that it does not exceed 600 mg/m^2:
139 mg ÷ 0.5 m^2 = 278 mg/m^2
This does not exceed the max dose of 600 mg/m^2, so 139 mg is acceptable.

Example 2:
Surface area = 1.2m^2 UN-corrected GFR = 50mL/min

$$\text{Total dose in mg/day} = \left\{\frac{50}{} + 15(1.2)\right\} \times 5$$

Dose = (50 + 18) x 5 = 340 mg/day

Double check dose to ensure that it does not exceed 600 mg/m^2:
340 mg ÷ 1.2 m^2 = 283 mg/m^2
This does not exceed the max dose of 600 mg/m^2, so 283 mg is acceptable.

5.1.2 Ototoxicity

Careful monitoring of children by expert audiologist and by serial audiometry throughout the treatment with carboplatin is recommended as clinically indicated. Otoacoustic emissions (OAE) are the clinical methodology of choice for initial testing. If these are normal, patients do not need further evaluation, and should be coded as having no hearing loss. If they are abnormal, then brainstem evoked auditory responses (BAER) or tone audiometry should be used to more specifically describe the hearing loss. A decrease in auditory acuity at frequencies above 4000 Hz is expected and does not constitute a contraindication to further therapy. For Grades 0, 1 and 2 ototoxicity (CTCAE) no dose modification is recommended. For Grade 3 toxicity, a 50% reduction should be made in the carboplatin dosage. For Grade 4 ototoxicity, carboplatin can be continued at 50% dose reduction or discontinued at the discretion of treating physician and family.

5.1.3 Allergic Reactions

Carboplatin allergic reactions may be managed with pre-medications such as diphenhydramine 1 mg/kg IV (maximum dose 50 mg), ranitidine 1 mg/kg IV (maximum dose 50 mg) and hydrocortisone 4 mg/kg IV (maximum dose 100 mg).

5.1.4 Hematologic Toxicity

If counts are slow to recover after Cycle A, use filgrastim (G-CSF) during subsequent Cycle A.

5.2 Etoposide

5.2.1 Nephrotoxicity

In patients with impaired renal function, the following initial dose modification should be considered based on measured creatinine clearance:

Measured CrCL	**> 50 mL/min/1.73m^2**	**15-50 mL/min/1.73m^2**
Etoposide Dose	100% of Dose	75% of Dose

Subsequent dosing should be based on patient tolerance and clinical effect. Data are not available in patients with creatinine clearances of < 15 mL/min and further dose reduction should be considered in these patients.

5.2.2 Hepatotoxicity

If the direct bilirubin is between 2 and 3 mg/dL, give 50% of the calculated dose of etoposide. If the direct bilirubin is > 3 mg/dL, hold the etoposide. Full dose may resume when the direct bilirubin has fallen to < 1.2 mg/dL.

5.2.3 Allergic Reactions

Etoposide allergic reactions may be managed with pre-medications such as diphenhydramine 1 mg/kg IV (maximum dose 50 mg), ranitidine 1 mg/kg IV

(maximum dose 50 mg), and hydrocortisone 1-2 mg/kg IV (maximum dose 100 mg), and by slowing the rate of the infusion. For those reactions, which are unable to be controlled with pre-medication and slowing of the rate of etoposide infusion, etoposide phosphate may be substituted in the same dose and at the same rate. Pre-medication for etoposide phosphate is recommended.

5.3 Ifosfamide

5.3.1 Hematologic

No modifications of subsequent chemotherapy cycles will be made for delayed recovery of neutrophil or platelet counts, following a prior cycle of Induction chemotherapy.

5.3.2 Hemorrhagic Cystitis

Microscopic Hematuria

For transient microscopic hematuria (no more than 2 abnormal urinalyses on 2 separate days during a cycle of therapy), there is no modification of the ifosfamide or mesna dose.

For persistent microscopic hematuria (> 2 abnormal urinalyses during a cycle of therapy), increase hydration to 3500-4000 mL/m^2/day. In addition, if mesna administration is oral or by intermittent intravenous bolus, convert to continuous intravenous mesna.

Gross Hematuria

All episodes of gross hematuria should be evaluated in conjunction with a pediatric surgery/urology consult. Further testing, such as cystoscopy, urine culture, excretory urogram, and voiding cystogram should be considered based on good clinical judgment.

For transient gross hematuria (only 1 episode, which clears to less than gross hematuria) during or following a cycle of therapy, hold ifosfamide until hematuria clears. When hematuria clears, restart at 50% of the previous ifosfamide dose. Use hydration of 3500-4000 mL/m^2/day and mesna at 100% of ifosfamide dose as a continuous infusion over 24 hrs/day. The ifosfamide dose may be escalated back to 100% if tolerated.

For persistent gross hematuria after completion of a cycle of therapy, hold subsequent ifosfamide until the urine clears to less than gross hematuria. Reinstitute ifosfamide at 50% of the initial dose, with hydration of 3500-4000 mL/m^2/day and the mesna at 100% of the ifosfamide dose administered as a continuous infusion over 24 hours. If this regimen is tolerated, the ifosfamide dose may be escalated back to the original dose (100%).

For persistent gross hematuria occurring during a cycle of ifosfamide, interrupt the ifosfamide. Withhold further ifosfamide until the next cycle of therapy or until urine clears. Reinstitute ifosfamide at 50% of the initial dose, with hydration of 3500-4000 mL/m^2/day and the mesna at 100% of the ifosfamide dose administered as a continuous infusion over 24 hours. If this regimen is tolerated, the ifosfamide dose may be escalated back to the original dose (100%).

For persistent gross hematuria on the mesna continuous infusion regimen, discontinue the ifosfamide.

5.3.3 Nephrotoxicity
In patients with a measured creatinine clearance <10 mL/min/1.73m^2, decrease dose by 25% (give 75% of initial dose).

5.3.4 Neurotoxicity
This is an organic brain syndrome that ranges from mild confusion and disorientation to seizures, ataxia, and coma. It may be aggravated by impaired renal function. It usually, but does not always, resolve spontaneously, and it may or may not recur with subsequent doses. If symptoms are mild and transient cycle may continue with strict avoidance of potentially aggravating co-administered medications such as sedatives and anticholinergic drugs. If Grade 4 neurotoxicity occurs during ifosfamide administration,
investigators may consider administration of methylene blue. Patients who have experienced mild symptoms (≤ Grade 2) may receive ifosfamide in subsequent cycles. If neurotoxicity > Grade 2 occurs or
symptoms are prolonged, delete ifosfamide from all subsequent cycles .

6.0 DRUG INFORMATION

See the consent document for toxicities. All other information is available on the COG website in the commercial agent monographs manual titled "Drug Information for Commercial Agents used by the Children's Oncology Group." This manual is provided under Standard Sections for Protocols at: https://members.childrensoncologygroup.org/prot/reference_materials.asp.

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

7.1 Required Clinical, Laboratory and Disease Evaluations During Protocol Therapy

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below. **Obtain other studies prior to start of phase unless otherwise indicated.**

STUDIES TO BE OBTAINED	Baseline	Prior to Each Cycle of Induction (Cycles A and B)	During Induction (Cycles A and B)	Completion of Induction (Day 21-35)	Following Second-Look Surgery	Within 2 Weeks Prior to Starting RT	During Radiation Therapy	Between 4 -6 Weeks following Completion of Therapy
History	X	X		X	X		X (Weekly If Clinically Indicated)	
Physical Exam (Ht, Wt, VS) with Neurologic Exam	X	X		X	X			X
Performance Status	X	X		X	X			X
CBC (differential, platelets)	X	X	X (Weekly)	X	X	X	X (Weekly If Clinically Indicated)	X
Urinalysis	X	X		X				X
Electrolytes (including BUN, Calcium, PO_4, Magnesium, Sodium, Potassium)	X	X	X (Weekly if Clinically Indicated)	X	X			X
Serum Creatinine, Creatinine Clearance or GFR	X			X				
Total protein, AST, ALT, albumin, bilirubin	X	X						X
Lumbar CSF Cytology[4]	X			X				X
CSF Markers (hCG, AFP)[6]	X			X				X
Serum markers (hCG, AFP)	X		X (After Cycles 2 and 4)	X	X	X		X
Brain MRI with and without gadolinium[1]	X		X (After Cycles 2 and 4)	X	X			X
Spine MRI	X[2]			X[5]				X[5]
Audiogram or BAER	X			X				X
Endocrine Function [3]	X			X				X
Pregnancy test (for females of childbearing potential)	X							

1- All patients must have a cranial MRI with and without gadolinium at diagnosis/prior to enrollment. If surgical resection is performed, patients must have pre-operative and post-operative cranial MRI with and without gadolinium. The post-operative brain

MRI should be obtained within 72 hours of surgery. If patient has a biopsy only, post-operative cranial MRI is recommended but not required.

2 - All patients must have a spine MRI with gadolinium obtained at diagnosis/prior to enrollment. Note: If the spine study is performed for the first time after surgical resection or biopsy, it is recommended to be obtained with and without gadolinium.

3 - Endocrine evaluation to include: Cortisol (8 AM), TSH, free T4, IGF1 and IGF BP3. Tanner Stage, LH, FSH, estradiol, and testosterone if child has precocious puberty before age 8 in girls or 9 in boys or for all patients age 11 or greater.

4 - Lumbar CSF cytology should be obtained unless medically contraindicated.

5 –Spinal MRI with gadolinium is sufficient.

6 – Lumbar CSF markers must be obtained unless medically contraindicated. If possible determine CSF markers and serum markers on the same day. If lumbar CSF markers are contraindicated, ventricular CSF markers are acceptable. In case CSF diversion and biopsy/surgery is combined, ventricular CSF should be collected first.

This table only includes evaluations necessary to answer the primary and secondary aims. Obtain other studies as indicated for good clinical care.

7.2 Required Observations Following Completion of Protocol Therapy

Observation	3 Months, 6 Months, 9 Months	Every 4 Months up to 24 Months (Months 12, 16, 20, 24) and at 30 Months	Annually up to 60 Months (Months 36, 48, 60)	At Relapse
Physical Exam with neurologic exam	X	X	X	X
Brain MRI with and without gadolinium	X	X	X	X
Spine MRI with gadolinium	X	X	X	X
Serum markers (hCG, AFP)	X	X	X	X
Lumbar CSF markers and cytology				X
Endocrine evaluation [4]			X	
Audiogram or BAER		X[2]	X[2]	
Neurocognitive Function (See ALTE07C1 Protocol and Section 16.0	X[3]	X[3]	X[3]	

1 - Lumbar CSF cytology and markers and serum markers should be obtained only at time of relapse unless medically contraindicated or if abnormal at completion of therapy.

2 – Obtain if clinically indicated or if abnormal at completion of therapy.

3 – Obtain at 9 months (± 3 months), 30 (± 3 months) and 60 months (± 3 months) post diagnosis.

4 - Endocrine evaluation to include: Cortisol (8 AM), TSH, free T4, IGF1 and IGF BP3. Tanner Stage, LH, FSH, Estradiol, and Testosterone if child has precocious puberty before age 8 in girls or 9 in boys or for all patients age 11 or greater.

See COG Late Effects Guidelines for recommended post treatment follow-up: http://www.survivorshipguidelines.org/

Note: Follow-up data are expected to be submitted per the Case Report Forms (CRFs) schedule.

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from Protocol Therapy

a) Progressive disease with increasing markers during Induction chemotherapy.

b) NGGCT (Stratum 1) patients with positive markers at the end of Induction chemotherapy or who have < PR after induction chemotherapy.

c) NGGCT (Stratum 1) patients with < PR after second-look surgery or any viable tumor (except mature teratoma) after second-look surgery

d) NGGCT (Stratum 1) patients who are unable to undergo second-look surgery due to safety or other reasons and do not meet criteria for CR/PR (imaging and tumor marrkers).

e) Germinoma (Stratum 2) patients with PD and positive markers at the end of Induction chemotherapy.

f) Germinoma (Stratum 2) patients who are unable to undergo second-look surgery due to safety concerns and they do not meet the criteria for at least PR with ≤ 1.5 cm residual disease without second-look surgery.

g) Germinoma (Stratum 2) patients with any viable tumor (except mature teratoma, fibrosis, scar or non-viable tumor) after second-look surgery

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

i) Completion of protocol therapy.

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

k) Development of a second malignancy.

l) Patient is enrolled but rechecked labs are outside the limits of eligibility prior to starting therapy. (See Section 3.2)

m) Radiotherapy cannot be initiated within 6 weeks after Day 1 of the last cycle of Induction chemotherapy or within 31 days after second-look surgery. (See Sections 15.2.3 and 15.2.4).

n) Progressive disease with positive or increasing markers at the end of Induction chemotherapy, following second-look surgery or during radiation therapy.

Patients who are off 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.

c) Patient enrollment onto another COG study with tumor therapeutic intent (eg, at recurrence).

d) Withdrawal of consent for any further data submission.

e) The fifth anniversary of the date the patient was enrolled on this study.

f) Patient did not receive protocol treatment after study enrollment.

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design

The primary objective of the NGGCT stratum 1 is to test whether the subset of NGGCT patients who have a CR or PR in response to induction chemotherapy or who undergo second-look surgery after induction therapy and are found to have only mature teratoma, residual scar or fibrosis can be safely treated with 30.6 Gy WVI and IFR boost up to 54 Gy. The "intent-to-treat" principle will be followed and any eligible patient who receives dose and volume reduced radiation therapy and is evaluable based on response to induction therapy will be included in the primary analysis. The number of patients enrolled in stratum 1 who fail to receive this reduced radiation therapy will also be reported

The primary objective of stratum 2 is to test whether the PFS distribution of localized primary CNS germinoma patients who present with serum and or CSF hCGβ ≤ 50mIU/ml is sufficient to support continued investigation of the proposed treatment regimen. The "intent-to-treat" principle will be followed and any eligible patient who receives dose-reduced radiation therapy will be included in the primary analysis. The number of patients enrolled in stratum 2 who fail to receive this reduced radiation therapy will also be reported.

In addition, for each stratum descriptive statistics will be provided reporting the proportion of patients who are classified as local, ventricular, distant or a combination of local, ventricular, and/or and distant failures based primarily on imaging evaluation of the neuraxis. See Section 15.12.

The first step in assessing primary objective 1.1.3, modeling neurocognitive function, as assessed on ALTE07C1, will be to monitor the rate of participation of eligible patients treated with dose and volume reduced radiation therapy in stratum 1 and dose-reduced radiation therapy in stratum 2. The same monitoring rule described below will be independently implemented for Stratum 1 and for Stratum 2.

Assessing neurocognitive function for patients treated on ACNS1123 will be considered feasible unless statistical evidence develops that fewer than 80% of patients who are eligible and evaluable for assessing primary objectives 1.1.1 or 1.1.2 and who are failure free at three years post initiation of therapy can be expected to have both 9-month and 30-month neurocognitive assessments on ALTE07C1. This rate of success will ensure that longitudinal modeling of neurocognitive function will provide viable historical controls for subsequent COG trials of these diseases. The rate of also achieving 60-month (5-year) neurocognitive assessments is not considered for monitoring feasibility, as the total study duration is only expected to be approximately seven years.

The statistical criteria for monitoring neurocognitive evaluations are based on a one-sided test ($\alpha = 0.025$) that the true, unknown, success rate is at least 80% ($\geq 80\%$) with 80% statistical power to detect that the success rate is 65%, which would be unacceptable. Assuming a binomial distribution, EAST5 was used to calculate the two stopping boundaries. If within a stratum, 9 (≤ 9) or fewer of the first 23 patients evaluable for feasibility (39.1%) have both 9 and 30 month evaluations (i.e. patients who are eligible and evaluable for assessing the primary objective and are more than 30 ± 4 months from

diagnosis), we will recommend to the COG DSMB that consideration be given to closing the stratum. The second boundary for recommending closing the stratum will be if 28 or fewer (≤28) of the initial 45 patients evaluable for feasibility (62.2%) enrolled in that stratum have both 9 and 30 month evaluations (i.e. patients who are eligible and evaluable for assessing the primary objective and are more than 30± 4 months from diagnosis). Otherwise accrual to the stratum will continue until the full cohort of patients required to address the primary objective assessing the 3-year progression-free survival rate has been achieved.

Our ability to address the secondary objectives depends upon whether the proposed treatment regimen is effective or not. Secondary objectives will be reported descriptively and as exploratory. Other than reports requested by the COG DSMB, secondary objectives will only be analyzed at the end of the trial.

1. The first secondary objective is to provide Kaplan-Meier estimates of distributions of PFS and overall survival for NGGCT patients.
2. The second secondary objective is to provide Kaplan-Meier estimates of the PFS and survival distributions of the cohorts of patients who present with a) non metastatic CNS Germinoma patients with hCGβ ≤ 50 mIU/ml and b) non metastatic CNS Germinoma patients with hCGβ > 50 mIU/ml and ≤ 100mIU/ml. These estimates will only be available to the COG DSMC until the trial is closed to accrual.

9.2 Sample Size and Study Duration

9.2.1 Stratum 1 NGGCT

In ACNS0122, COG institutions enrolled 79 eligible patients with localized disease over a period of 53 months. Of these 79 patients, 49 (95% lower confidence bound = 53%) would have been eligible based on response to induction therapy to address the primary study objective of this trial for an expected accrual rate of approximately 11.1 patients per year. Thus, we expect that approximately 7 years will be required to accrue the required 77 eligible patients evaluable for the primary objective.

9.2.2 Stratum 2 Germinoma

Based on the publication by Keene et al, the 95% confidence interval estimate of the incidence of CNS germinoma in children 4 to <18 years of age is (0.48, 0.91). [67] We assume that this estimate holds for 5 to 19 year olds. Canada and US population estimates for 5 to 19 year olds are 6.02 and 61.7 million, respectively. Thus, annually we estimate that there are 32.5 to 61.6 diagnoses of CNS germinomas in patients 5 to 19 years of age. Again based on Keene et al, approximately 77% of patients with CNS germinomas will be diagnosed with localized disease and approximately 75% will present with serum and CSF hCGβ ≤ 50mIU/ml. [67] Assuming that 80% of eligible patients would consent to enrolling on this study, we estimate that the annual accrual for patients eligible for the primary study objective will be between 15 and 28 patients. Since 64.7% of eligible patients are expected to be evaluable for the primary objective, annual accrual of eligible, evaluable patients will be between 10 and 18 patients.

Due to the excellent accrual rate of germinoma patients within the initial 2.5 years of study opening (accrual of 80 patients within 27 months), we expect that approximately 5 years will be required as originally estimated to accrue the required 79 eligible patients evaluable for the primary objective. Note that assessing whether the accrual rate is adequate should not begin until one year after the protocol has been released to COG institutions for submission to their Institutional Review Boards (IRB). Receiving IRB approval takes significant time and thus accrual during the first year will no doubt be much less than projected; thus, assessment will begin with the completion of year two.

9.2.3 Total Accrual

Considering 77 eligible, evaluable patients will be required for Stratum 1 and 79 eligible, evaluable patients for Stratum 2, with a 10% ineligible rate, the maximum number of patients expected to be accrued is 275 patients.

As of Amendment #1A, for Stratum 1, the original estimate of the study duration was mistakenly based on the fact that all eligible patients enrolled on Stratum 1 would be evaluable for addressing the primary objective. However, the Stratum 1 primary objective will be addressed only by eligible patients who achieve an objective response and hence qualify to receive reduced radiation therapy. In reality, based on the results from the preceding ACNS0122 study, we had expected that approximately 62% of Stratum 1 eligible patients would experience a CR or PR and would receive reduced radiation therapy. Considering that 77 eligible patients who achieve a CR or PR and receive reduced radiation therapy are required to address the primary objective of Stratum 1, we will need to increase accrual to approximately 125 patients.

For Stratum 2, in order to estimate the study duration, there was no information on which we could estimate the proportion of eligible patients that would experience a complete response or continued complete response and contribute to addressing the primary objective. Seventy-nine (79) eligible, evaluable patients are required to address the primary objective. Currently, based on the ACNS1123 data through 31 December 2013, we estimate that approximately 64.7% of Stratum 2 eligible patients will experience a CR or CCR, receive reduced radiation therapy and contribute to addressing the primary objective. Thus, we need to accrue a total of 123 eligible patients to Stratum 2.

Assuming that the expectation for 62% of Stratum 1 eligible patients and 64.7% of Stratum 2 eligible patients will contribute to addressing the primary objectives is realized, we will need to accrue 248 (125+123) patients and assuming a 10% ineligibility rate, the maximum number of patients expected to be accrued is 275.

9.3 Methods of Analysis

9.3.1 Stratum 1 NGGCT

This study will be designed based on the observed outcome for patients treated on ACNS0122. Of 102 eligible patients treated on ACNS0122, 79 (77.5%) were determined to have localized disease. Thirty-two of the 79 (40.5%) patients achieved a CR (N=25) in response to induction therapy or were found on second-

look surgery to have a mature teratoma, residual scar or fibrosis (N= 7). Based on the ACNS0122 data frozen as of June 30, 2011, the 3-year PFS rate for these 32 patients is 90.6% (SE=5.2%) and follow-up was current for all patients. No patient is censored within two years of initiating therapy and 5 patients continue to be followed in their third year. Seventeen of the 79 (21.5%) patients achieved a PR in response to induction therapy and the 3-year PFS rate for these patients is 94.1% (SE=5.7%) with no patient censored within two years of initiating therapy and 2 patients continuing to be followed in their third year. The 3-year EFS point estimate (95% confidence interval estimate) for the 32 CR and 17 PR patients are 90.6% (73.7%, 96.9%) and 94.1% (65.0%, 99.2%), respectively. Thus the 3-year PFS rate for these two cohorts of patients treated on ACNS0122 are both excellent and similar supporting our decision to combine the groups in our study of reduced irradiation. The observed 3-year PFS rate for the combined cohort of 49 patients (32+17) is 91.8% (SE=3.9%).

The historical data from the COG trial ACNS0122 shows that for the 102 patients with localized NGGCT, all failures have occurred within two years of initiating treatment with a single exception of a patient who failed at approximately six years post initiation of treatment. In fact, most failures occurred within one year of initiating treatment. As indicated above, the outcome for the subset of 49 patients treated on ACNS0122 who would have been eligible for treatment on ACNS1123 is exceptional with only three failures in the first year and one in the second year of follow up. Thirty-eight patients have been followed for more than three years. With so few failures in the historical data, the usual time-to-event distributions, exponential, Weibull etc., are difficult to characterize and to assess for adequacy of fit; so the Study Committee has no estimate of a hazard rate and clearly no estimate of median progression-free survival. The binomial distribution appeared to be the best distribution on which to design this trial reflecting the fact that with rare exception all failures are expected to occur early. The binomial distribution parameterized by the 3-year PFS rate is expected to be sufficient to capture virtually all failures and reflects the fact that the investigators are confident that all patients will be successfully followed for at least three years. This method requires that no patient be lost to follow up within the first three years. All patients who fail to be evaluated for progression at the 3-year mark will be included in the primary analysis as failures. The Principal Investigators are committed that no patient be lost to follow up within three years of initiating treatment.

Considering the current results of ACNS0122, a true, unknown 3-year PFS rate of 0.82 for this reduced therapy approach is considered unacceptable by the study team. The sample size calculation will be based on the binomial distribution testing that the true, unknown 3-year PFS rate is at most 82% (null hypothesis: ≤ 0.82) and powered to detect that the 3-year PFS rate is really 93% (0.93). East 5.3© was used to calculate the require sample size of 77 patients. This design will reject the null hypothesis if at least 69 patients (≥ 69) are progression free after three years and conclude that reduced therapy is acceptable. Due to the discrete distribution, the actual type I error rate is 0.0492 (probability of falsely concluding that the treatment is effective when the true 3-year PFS rate is 0.82) and statistical power is 0.911 (probability of correctly concluding that the treatment is effective when the true 3-year PFS rate is 0.93).

In order for the reduced therapy approach to be considered to have sufficient merit for continued investigation, our design requires a statistically significant result – p-value<0.0492. The null hypothesis must be rejected otherwise this approach will have to be reconsidered.

Due to the expected accrual rate, expected low failure rate and three year PFS endpoint, even one interim analysis for futility that would stop accrual early is not feasible. Note that interim analyses would be restricted to patients who are documented failures within three years of initiation of treatment and those patients followed for three years failure free. Thus, no formal futility interim analysis is planned. However, if 9 patients are documented to have failed (progressed or lost to follow up) before three years of follow up and fewer than 77 patients eligible for the primary analysis have begun treatment, accrual will be suspended until the COG Data Safety Monitoring Board (DSMB) has had the opportunity to review all data.

9.3.2 Stratum 2 Germinoma

The outcome for patients with localized germinoma treated with CSI is even better than the outcome for patients with NGGCT discussed above. Huh, Maity and Bamberg report 10-year PFS of 96.6% (n=32); 5-year PFS of 100% (n=39); and 5-year PFS of 88% (n=49), respectively.[33-35] The four relapses in the Bamberg cohort were all within three years of initiating therapy. Calaminus reported an EFS rate of 97 ± 2% for 128 patients with localized germinoma treated with CSI. Thus, a similar statistical approach is justified for evaluating reduced therapy for patients with localized germinoma. The binomial distribution seems most appropriate for the design for this stratum, as again the usual time-to-event distributions, exponential, Weibull, etc. cannot be well-characterized based on the available data. The 3-year PFS rate was chosen as all failures are expected within three years of initiating therapy and we will successfully follow all patients for at least three years.

Based on the results of the SIOP-96, SFOP trial and Japanese studies, our approach will be considered acceptable if there is statistical evidence that the true, unknown 3-year PFS rate is greater than 0.87 (> 87%). Thus, a one-sided test will be used with a type I error rate of 0.10 ($\alpha = 0.10$) and 90% statistical power ($\beta = 0.10$), if the true 3-year PFS rate is 95%. Since this approach offers the potential for superior quality of life for surviving patients who are spared exposure to highly effective cranial spinal irradiation that has long term consequences for survivors, we have set the statistical power at 90%.

The sample size calculation will be based on the binomial distribution testing that the true, unknown 3-year PFS rate is at most 87% (null hypothesis: ≤ 0.87) and powered to detect that the 3-year PFS rate is really 95% (0.95). This method requires that no patient be lost to follow up within the first three years. All patients who fail to be evaluated for progression at the 3-year mark will be included in the primary analysis as failures. The Principal Investigators are committed that no patient be lost to follow up within three years of initiating treatment. East 5.4© was used to calculate the require sample size of 79 patients. This design will reject the null hypothesis if at least 73 patients (≥ 73) are progression free after three years. This approach was selected to minimize the number of patients with this rare

disease that would be required to address the primary study objective with statistical confidence even though considerable effort will be required to assure that no patient is lost to follow up within three years of initiating treatment. The study team is confident that this is possible.

In order for the reduced therapy approach to be considered to have sufficient merit for continued investigation, the null hypothesis must be rejected otherwise this approach will have to be reconsidered.

Due to the expected accrual rate, expected low failure rate and 3-year PFS endpoint, even one interim analysis for futility that would stop accrual early is not practical. If at any point in the trial, 7 patients are documented to have failed (progressed or been lost to follow up) before three years of follow up and fewer than 79 patients eligible for the primary analysis have begun treatment, accrual will be suspended until the COG DSMB has had the opportunity to review all data.

9.3.3 Longitudinal Modeling of Neurocognitive Function (Cognitive, Social and Behavioral)

These analyses will be conducted independently for Stratum 1 (NGGCT) and Stratum 2 (Germinoma) patients. To be included in the analyses, patients must have the 9-month baseline assessment and at least one of either the 30-month or 60-month assessments.

The ALTE07C1 standard neuropsychological and behavioral battery focuses on three cognitive domains: intelligence, attention, and memory, as well as broad domains of social, emotional, and behavioral functioning. Data for all assessments will be available as standardized t-scores. The change over time for each component of the neuropsychological testing will be estimated using Generalized Estimating Equation (GEE); [82] with the standardized t-scores as the dependent variable and the assessment times as a covariate. For neuropsychological components for which some patients are missing data at one of the three assessments, Weighted GEE [83-84] will be used to address the missingness under the assumption that the data are missing at random (MAR).

GEE models will be used to explore associations of changes over time with factors such as gender, age at initiation of radiation therapy, tumor location, surgical intervention, etc.

9.4 Gender and Minority Accrual Estimates

The gender and minority distribution of the study population is expected to be:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	8	3	11
Not Hispanic or Latino	128	136	264
Ethnic Category: Total of all subjects	136	139	275
Racial Category			
American Indian or Alaskan Native	3	0	3
Asian	3	3	6
Black or African American	14	8	22
Native Hawaiian or other Pacific Islander	3	3	6
White	113	125	238
Racial Category: Total of all subjects	136	139	275

This distribution was derived from ACNS0122.

10.0 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize version 4.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Additionally, toxicities are to be reported on the appropriate case report forms.

Please note: 'CTCAE v4.0' is understood to represent the most current version of CTCAE v4.0 as referenced on the CTEP website (ie, v4.02 and all subsequent iterations prior to version 5.0).

10.2 General Methodology for Determining Tumor Measurements

2D (area) tumor dimensions are determined by measurement of the longest tumor dimension and its perpendicular for each target lesion. 3D (volume) tumor dimensions are determined by measurement of the longest tumor dimension and its perpendicular and the length (perpendicular to the plane of the axial measurement) for each target lesion. Regarding MRI imaging, the radiologist at each institution may select whatever sequence best highlights the tumor (T1 enhanced or T2 weighted or FLAIR images) and the same sequence should be used for serial measurements. Response determination will be based on a comparison of a 2D (area:W x T – see below) 3D (volume; (W x T x L– see below) between the baseline assessment and the study date designated in the follow-up Report Form. Reports for the

follow-up exams should reiterate the measurements obtained at baseline for each target lesion. Newly occurring lesions should also be enumerated in these reports.

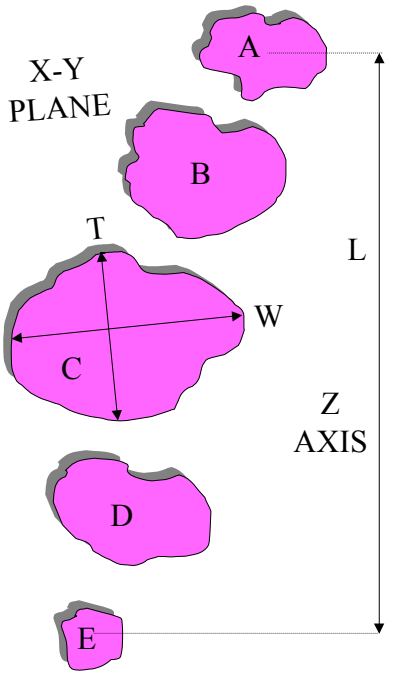
Tumor response criteria are determined by changes in size using the longest tumor dimension, and its perpendicular +/- length. Either T1 or T2 weighted images are used - which ever gives the best estimate of tumor size. The following section describes the methodology. (See Figure 10.1 below for illustration)

1. For MRI imaging the longest diameter can be measured from the axial plane or the plane, provided the same plane is used in follow ups. This longest measurement of the tumor is referred to as the width (W).
2. The perpendicular measurements should be determined - transverse (T) measurement, perpendicular to the width in the selected plane.
3. The length is then measured as the perpendicular to the plane defined by measurements in 1 and 2.
4. The cystic or necrotic components of a tumor are typically not considered in tumor measurements. Therefore only the solid component of cystic/necrotic tumors should be measured. If cysts/necrosis composes the majority of the lesion, the lesion may not be "measurable".

Options:

- if the cyst/necrosis is eccentric, the W and T (and L) of the solid portion should be measured, the cyst/necrosis excluded from measurement
- if the cyst/necrosis is central but represents a small portion of the tumor (< 25%), disregard and measure the whole lesion
- if the cyst/necrosis is central but represents a large portion of the tumor, identify a solid aspect of the mass that can be reproducibly measured

Figure 10.1: COG Guidelines for Measurement of Tumor Size



COG GUIDELINE: TUMOR SIZE MEASUREMENT BASED ON CROSS-SECTIONAL IMAGING

• A, B, C, D, & E are contiguous parallel slices in the X-Y plane (usually axial) showing the tumor
• W and T are the maximal perpendicular diameters on the slice (C in this example) showing the largest surface area
• Tumor length in the Z-axis (L) (perpendicular to X-Y plane) can be obtained either by the [a] (difference in table position of the first and last slices showing the tumor + one slice thickness), or [b] the product of (slice thickness + gap) and the number of slices showing the tumor

5. Overall Response Assessment

The overall response assessment takes into account response in both target lesion and the appearance of new lesions, where applicable, according to the criteria described in the table below. The overall response assessment is shown in the last column, and depends on the assessments of target and new lesions in the preceding columns.

Target Lesions	**New Lesions**	**Overall Response**
CR	No	**CR**
PR	No	**PR**
SD	No	**SD**
PD	Yes or No	**PD**
Any	Yes or No	**PD**
Any	Yes	**PD**

CR – Complete Response
PR – Partial Response
SD – Stable Disease
PD – Progressive Disease
IR – Incomplete Response

The sections that follow discuss the selection and evaluation of each of these types of lesions.

10.3 Selection of Target Lesions

1. For most CNS tumors, only one lesion/mass is present and therefore is considered a "target" for measurement/follow up to assess for tumor progression/response.
2. In case of a bifocal lesion both lesions should be selected as "target" lesions.
3. The lower size limit of the target lesion(s) should be at least twice the thickness of the slices showing the tumor to decrease the partial volume effect (e.g. 8 mm lesion for a 4 mm slice).

10.4 Response Criteria for Target Lesions

1. Response criteria are assessed in 3 (volume) (or 2 (area) if 3 not possible) dimensions – the product of W x T x (L).
2. To assess response/progression, the ratio is calculated (x 100 = %):

$$\frac{W \times T \times (L) \text{ (current scan)}}{W \times T \times (L) \text{ (reference scan)}}$$

3. Development of new disease or progression in any established lesions is considered progressive disease (PD), regardless of response in other lesions – e.g. even when multiple lesions show opposite responses, the progressive disease takes precedence.
4. For purposes of this study, response criteria for target lesions are:

Complete Response (CR): Complete disappearance of visible disease on imaging allowing for minimal residual disease/enhancement ≤ 0.5 cm maximal dimension in suprasellar or ≤ 1 cm in pineal locations.

Continued complete response (CCR): Continuing absence of radiographically identifiable disease allowing for minimal residual disease/enhancement ≤ 0.5 cm maximal dimension in suprasellar or ≤ 1 cm in pineal locations.

Partial response (PR): > 0.5 cm dimension residual in the suprasellar area or > 1 cm residual in case of pineal involvement after completion of chemotherapy, but ≥ 65% decrease in the sum of the products of the three perpendicular diameters (volume) of all target lesions (up to 5), taking as reference the initial baseline measurements.

Stable Disease (SD): Neither sufficient decrease in the sum of the products of the three perpendicular diameters of all target lesions to qualify for PR (taking as reference the initial baseline measurements), nor sufficient increase in a single target lesion to qualify for PD, (taking as reference the smallest disease measurement since the treatment started) and residual disease after chemotherapy of > 1.5 cm maximal diameter.

Progressive Disease (PD): 40% or more increase in the product of perpendicular diameters (volume) of ANY target lesion, taking as reference the smallest product observed since the start of treatment, or the appearance of one or more new lesions.

***In the circumstance that 3-D measurement cannot be determined, maximal diameter in a 2-D measurement (area) would be used to evaluate response: TxW (product of the longest diameter and its longest perpendicular diameter)**

Complete response (CR): Complete disappearance of visible disease on imaging allowing for minimal residual disease/enhancement ≤ 0.5 cm maximal dimension in suprasellar or ≤ 1 cm in pineal locations.

Continued complete response (CCR): Continuing absence of radiographically identifiable disease allowing for minimal residual disease/enhancement ≤ 0.5 cm maximal dimension in suprasellar or ≤ 1 cm in pineal locations.

Partial response (PR): > 0.5 cm maximal dimension residual in the suprasellar area or > 1 cm residual in case of pineal involvement after completion of chemotherapy, but more than ≥ 50% decrease in 2-D (area) measurement.

Stable disease (SD): Decrease in < 50% of all target lesions and residual disease after chemotherapy of >1.5 cm maximal diameter.

Progressive disease (PD): Defined as ≥ 25% increase 2-D (area) of target lesion(s) or development of any new lesions irrespective of the response of the initial lesions.

5. Defining Tumor Marker Response

Patients tumor marker in serum and CSF must remain negative (AFP, hCGβ) or become negative (AFP, hCGβ) at completion of chemotherapy. Patients with PD and increasing levels of hCGβ or AFP after completion of 2, 4 or 6 courses of chemotherapy will come off protocol.

10.5 Retrospective Response Review

MRI imaging for all patients on study will undergo retrospective central review following the completion of treatment. Results of the retrospective review will not be returned to the site. See Section 14.4 for imaging central review requirements.

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 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.

11.2 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 known toxicities for each commercial agent as provided in the Drug Information for Commercial Agents Used by the Children's Oncology Group posted on the COG website; or***
- ***the drug package insert.***

Secondary Malignancy

A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (eg, treatment with investigational agent/intervention, radiation or chemotherapy). A metastasis of the initial neoplasm is not considered a secondary malignancy.

All secondary malignancies that occur following treatment need to be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy

- Myelodysplastic syndrome
- Treatment related secondary malignancy

11.3 Reporting of Adverse Events for Commercial Agents –via CTEP-AERS

Expedited AE reporting must use CTEP-AERS (Adverse Event Expedited Reporting System), accessed via https://eapps-ctep.nci.nih.gov/ctepaers

Commercial reporting requirements are provided in Table B. The commercial agent(s) used in this study are listed in the front of this protocol immediately following the Study Committee roster.

- COG requires the CTEP-AERS report to be submitted **within 7 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.

CTCAE term (AE description) and grade: The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting and are located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE.

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.

CTEP-AERS 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			CTEP-AERS
Possible, Probable, Definite	CTEP-AERS		CTEP-AERS

[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 CTEP-AERS.

11.4 Routine Adverse Event Reporting

Note: The guidelines below are for routine reporting of study specific adverse events on the COG case report forms and do not affect the requirements for CTEP-AERS reporting.

The NCI defines both routine and expedited AE reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include all toxicities reported via CTEP-AERS and all Grade 3 and higher Adverse Events.

12.0 STUDY REPORTING AND MONITORING

The Case Report Forms and the submission schedule are posted on the COG web site with each protocol under "*Data Collection/Specimens*". A submission schedule is included.

12.1 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.

12.2 Data and Safety Monitoring Committee

To protect the interests of patients and the scientific integrity for all clinical trial research by the Children's Oncology Group, the COG Data and Safety Monitoring Committee (DSMC) reviews reports of interim analyses of study toxicity and outcomes prepared by the study statistician, in conjunction with the study chair's report. The DSMC may recommend the study be modified or terminated based on these analyses.

Toxicity monitoring is also the responsibility of the study committee and any unexpected frequency of serious events on the trial are to be brought to the attention of the DSMC. The study statistician is responsible for the monitoring of the interim results and is expected to request DSMC review of any protocol issues s/he feels require special review. Any COG member may bring specific study concerns to the attention of the DSMC.

The DSMC approves major study modifications proposed by the study committee prior to implementation (eg, termination, dropping an arm based on toxicity results or other trials reported, increasing target sample size, etc.). The DSMC determines whether and to whom outcome results may be released prior to the release of study results at the time specified in the protocol document.

13.0 SURGICAL GUIDELINES

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

13.1 Pre-operative Considerations

The majority of patients with primary intracranial germinoma or NGGCT will present with mass lesions in either the pineal and/or suprasellar regions. Other less common locations include the thalamus/basal ganglia and fourth ventricle. Patients with primary tumors in the pineal region are likely to present with hydrocephalus. The neurosurgeon must consider the following goals in the initial management of patients suspected of harboring a primary germ cell tumor.

13.1.1 Neuroimaging

Cranial MRI

All patients must have a cranial MRI with and without gadolinium at diagnosis/prior to enrollment. If surgical resection is performed, patients must have pre-operative and post-operative cranial MRI with and without gadolinium. The post-operative brain MRI should be obtained within 72 hours of surgery. If patient has a biopsy only, post-operative cranial MRI is recommended but not required.

Spinal MRI

All patients must have a spine MRI with gadolinium obtained at diagnosis/prior to enrollment.

Note: If the spine study is performed for the first time after surgical resection or biopsy, it is recommended to be obtained with and without gadolinium.

13.1.2 Medications

- Corticosteroids: Patients with large tumors and those with non-communicating hydrocephalus may benefit from high doses of corticosteroids such as dexamethasone (0.25-1.0 mg/kg/day) in divided doses every 6-8 hours. Appropriate endocrine tests should be drawn in consultation with the pediatric endocrine consultant prior to initiating corticosteroid therapy.
- Anticonvulsants: The use of prophylactic anticonvulsants in patients with CNS germ cell tumors in typical locations such as the suprasellar and pineal regions is not encouraged. Seizures are rare following endoscopic third ventriculostomy or intraventicular tumor biopsy. Prophylactic anticonvulsants may be administered prior to craniotomies and corticectomies depending on institutional policy.

13.1.3 Hydrocephalus

- Most patients with pineal region tumors will present with a non-communicating hydrocephalus due to obstruction of flow at the level of midbrain through the aqueduct of Sylvius.
- A communicating hydrocephalus may arise as a consequence of diffuse leptomeningeal metastases. The management of hydrocephalus will relate to the severity of symptoms of raised intracranial pressure and the clinical response to corticosteroids.
- The preferable management for patients with a pineal region tumor and obstructive hydrocephalus is a third ventriculostomy at the time of endoscopic biopsy.
- The routine placement of a VP shunt is not recommended.

13.1.4 Tumor Sampling and Resection

See Section 3.2.2 regarding eligible diagnosis.

- It is highly desirable to first confirm the diagnosis on frozen section in the operating room and then to obtain sufficient tissue for flash freezing (biology studies) and formalin fixation (complete immunohistological characterization).
- Radical resection for reduction of tumor burden is discouraged given the rapidity with which responses are expected with either radiation therapy or chemotherapy.

13.1.5 Intra-operative CSF sampling

- For patients undergoing an endoscopic procedure, it is highly desirable that intraventricular CSF sample to be obtained prior to biopsy and sent for cytology, hCG and AFP. The ventricular CSF should be obtained before fluid is instilled for irrigation.
- Lumbar CSF should be obtained (within 10-14 days after surgery if applicable) for cytopathology prior to enrollment unless medically contraindicated.

13.2 Operative Management

13.2.1 Endoscopy

- It is recommended that the endoscope be used for intraventicular tumor biopsy and for performance of a third ventriculostomy, if needed.

- Normal sized ventricles do not preclude the use of the endoscope for tumor biopsy if stereotactic guidance is available. The endoscope should be coupled to the frameless navigation system. The visual documentation of seeding, undetectable at the level of sensitivity of neuroimaging, will be documented, but will not alter radiation treatment.

13.2.2 Other Operative Approaches

It is recognized that some tumors may not be easily biopsied by endoscopic techniques and alternate approaches may be appropriate, depending on the anatomy of the tumor and institutional expertise. These include the following:

- Stereotactic needle biopsy
  Image-guided frame-based techniques are preferred at some sites for appropriately selected tumors. Careful planning of the trajectory is essential to minimize the risk of injury to deep venous and arterial structures.

- Transphenoidal procedures
  The transphenoidal approach may be the preferred method to biopsy a isolated suprasellar tumor, especially if a radical resection is not required. The morbidity of this approach is less than a craniotomy.

- Open craniotomy
  If the above techniques are not deemed feasible or fail to yield diagnostic tissue, an open craniotomy would be appropriate as a means for establishing the diagnosis of a germ cell tumor. The operative approach would be determined by the lesion location and geometry.

13.2.3 Ancillary Procedures

- External ventricular drain (EVD)
  In some circumstances an EVD may be necessary for monitoring intracranial pressure or temporary control of hydrocephalus.

- Septostomy
  If the tumor is producing hydrocephalus by obstructing a lateral ventricle at the level of the foramen of Monro, a third ventriculostomy may not be possible. In such cases, a septostomy may allow a communication to be established between the two lateral ventricles and permit a tumor biopsy at the same procedure.

13.2.4 Internal Shunts
The routine use of permanent internal shunts is discouraged. However, a ventriculo-peritoneal shunt may be necessary in specific circumstances when a third ventriculostomy is not feasible or contraindicated, i.e., in the presence of tumor deposits on the floor of the third ventricle or communicating hydrocephalus.

13.3 Management of Complications

- Peri-surgical complications include hemorrhage, infection, seizures, and neurological injury.
- Significant complications will delay the implementation of adjuvant therapy and may preclude protocol eligibility.
- The patient must be ready to begin protocol therapy within 31 days of surgery. Readiness assumes significant recovery from peri-operative complications and absence of any wound dehiscence, CSF leakage, uncontrolled hydrocephalus or uncontrolled life-threatening endocrine deficiency.

13.4 Second-Look Surgery

- The presence of residual or progressive disease after the completion of induction chemotherapy in patients following 4 or 6 (NGGCT) cycles of chemotherapy warrants consideration of a "second-look" surgical procedure.
- All differential diagnostic concerns must be considered to include: a non-germinomatous germ cell component, mature teratoma, a non-protocol tumor and scar/fibrosis.
- Appropriate management will depend on narrowing this differential. An open craniotomy may be the preferred procedure since a radical resection of residual tumor may be therapeutic.[4]

14.0 IMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

14.1 Timing of MRIs

Cranial MRI

All patients must have a cranial MRI with and without gadolinium at diagnosis/prior to enrollment. If surgical resection is performed, patients must have pre-operative and post-operative cranial MRI with and without gadolinium. The post-operative brain MRI should be obtained within 72 hours of surgery. If patient has a biopsy only, post-operative cranial MRI is recommended but not required.

Spinal MRI

All patients must have a spine MRI with gadolinium obtained at diagnosis/prior to enrollment.

Note: If the spine study is performed for the first time after surgical resection or biopsy, it is recommended to be obtained with and without gadolinium.

To document localized disease, standard cranial MRI with and without gadolinium and a spine MRI with gadolinium must be performed at the following time points:

Brain

- Pre-operative and Post-operative (if applicable)
- Baseline (Prior to enrollment)
- After Cycles 2 and 4 of Induction
- Completion of Induction
- After Second-Look Surgery (if done)
- End of Therapy

Spine

- A spine MRI obtained preoperatively can be obtained with gadolinium only. If the spine study is performed for the first time post-op, it is recommended to be performed without and with gadolinium
- Completion of Induction
- End of therapy

14.2 MRI Guidelines for Brain/Spine Tumors

For recommended brain/spine imaging (1.5 Tesla), required and optional sequences and technical details, see the COG CNS Imaging Guidelines posted on the COG member website at: https://members.childrensoncologygroup.org/_files/reference/RefMaterial/COGCNSImagingGuidelines6_4_10.pdf.

14.3 Tumor Response Assessment

For the response assessments, MRI scans obtained at the time-points during protocol therapy (see Section 10.4) will be compared to the baseline MRI scan. **Exception:** In cases of progressive disease, the reference scan should be the MRI with the smallest product observed since the start of treatment).

14.4 Retrospective Central Review

A retrospective central review of imaging will be performed for all patients enrolled on ACNS1123. Results of the retrospective review will not be returned to the site. Submit the following studies that have not already been submitted for the RT on-treatment review with their corresponding reports for central review at the completion of treatment or when the patient is removed from protocol therapy or at the time of progressive disease/recurrence.

Brain

- Baseline
- Pre and Post Operative scan (if applicable)
- End of Induction
- Post Second-look Surgery
- End of Therapy
- Progressive Disease/Recurrence

Spine

- Progressive Disease/Recurrence

14.4.1 Address Information

Submission of Diagnostic Imaging data in digital format is required. Digital files must be in DICOM format. These files can be submitted via sFTP. Information for obtaining an sFTP account and submission instructions can be found at www.QARC.org. Follow the link labeled digital data. Alternatively, if sFTP is not feasible, the imaging may be burned to a CD and mailed to IROC RI (QARC) at the address below. Multiple studies for the same patient may be submitted on one CD; however, please submit only one patient per CD. Sites using Dicommunicator may submit imaging via that application. Contact IROC RI (QARC) with questions or for additional information.

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

IROC RI (QARC)
640 George Washington Highway
Building B, Suite 201
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601

15.0 RADIATION THERAPY GUIDELINES

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG administrative Policy 5.14 (except where explicitly prohibited within the protocol).

Radiation Therapy (RT) can only be delivered at approved RT facilities (COG administrative policy 3.9).

15.0 General Guidelines

The indications for radiation therapy on this protocol will be based on response to induction chemotherapy. All patients will receive radiotherapy after induction chemotherapy, unless recommended to undergo second surgery. If second-look surgery is performed, radiation therapy will be performed following the surgery. The radiation dose and fields will be based on both histology and response to induction chemotherapy or results from second surgery. This study specifies a 5 mm clinical target volume margin and mandates the use of CT-MR registration to define the target volumes. The allowed treatment methods are restricted to conformal or intensity-modulated radiation therapy using photons or proton beam therapy and electronic data submission is required.

15.0.1 Treatment Planning Specifics

The guidelines for this study were developed by COG radiation oncology investigators and approved by the radiation oncology discipline committee. This study stratifies NGGCT to Stratum 1 and Germinoma to Stratum 2. Both strata include whole ventricular irradiation followed by boost irradiation of the primary site. The prescribed doses to the ventricular and boost volumes are fixed for Stratum 1 and vary according to response for Stratum 2. The whole ventricular volume should be contoured according to an atlas approved by the radiation oncology committee.

15.0.2 Required Benchmark and Questionnaires

Radiation therapy will be administered using protons or photons. Required photon methods include 3D-conformal radiation therapy (3D-CRT) and intensity modulated radiation therapy (IMRT). Centers participating in this protocol using 3D-CRT are required to complete the 3D benchmark; those using IMRT must complete the IMRT questionnaire and benchmark or phantom and those using protons must complete the proton benchmark and questionnaire. All centers participating in this protocol must complete the IROC RI (QARC) CT/MR image fusion benchmark. Benchmark materials and questionnaires may be obtained from the IROC RI (QARC) (www.qarc.org) and must be submitted before patients on this protocol can be evaluated. For information regarding the IMRT phantoms, please contact the RPC (http://rpc.mdanderson.org/rpc).

15.0.3 Guidelines and Requirements for the Use of IMRT

Investigators using IMRT will be required to comply with the guidelines developed for the use of IMRT in National Cancer Institute sponsored

cooperative group trials. These guidelines are available through www.qarc.org. These guidelines require that the protocol explicitly state their requirements and methods for localization and immobilization; the use of volumetric imaging; target and organ motion management; nomenclature, definitions and rationale for targets and organs at risk; target volume coverage and normal tissue dose constraints; effects of heterogeneity in tissues; and quality assurance.

15.0.4 Guidelines and Requirements for the Use of Proton Beam Therapy

Proton therapy may be used to deliver radiation therapy on this protocol. The proton therapy method will be limited to passive scattering and uniform scanning. Investigators using proton beam radiation must comply with the Advanced Technology Consortium proton therapy guidelines available through www.qarc.org. These guidelines specify the following for the participating institution: both passive and scanned beams may be used, but the Radiologic Physics Center must review and credential the specific beam line delivery parameters. Dose reporting will be in Gy (RBE). Radiation doses shall be prescribed protocol specified definitions for gross (GTV) and clinical (CTV) target volumes. For set-up uncertainties and target motion, additional margin, smearing, range of modulation will be added on a per beam basis. The proton institution is required to participate in on-site and remote review according to COG guidelines.[79-81]

15.1 Indications for Radiation Therapy

15.1.1 Stratum 1

Stratum 1 patients with NGGCT enrolled on this protocol will receive 6 cycles of induction chemotherapy. If there is a CR by neuroimaging or PR with marker normalization following chemotherapy, radiation therapy will follow the 6th cycle of chemotherapy. If there is PR, SD or PD to chemotherapy, second-look surgery is recommended. If surgery results in a PR or CR and tumor marker normalization, radiation therapy will follow surgery. If there is <PR or positive markers after 6 cycles of induction or if there is residual viable tumor (except mature teratoma) at the time of second-look surgery, the patient will be removed from protocol therapy.

15.1.2 Stratum 2

Stratum 2 patients with Germinoma enrolled on this protocol will receive 4 cycles of induction chemotherapy. If there is a CR or CCR to chemotherapy, radiation therapy will follow the 4th cycle of chemotherapy. If there is PR, SD, or PD after chemotherapy, second surgery is highly recommended. If mature teratoma or scar/fibrosis/non-viable tumor is found on second-look surgery, then radiation therapy will follow surgery. If surgery identifies viable tumor other than mature teratoma, the patient will be removed from protocol therapy. Patients with positive markers after induction chemotherapy will be removed from protocol therapy.

If there is SD or PR after chemotherapy (> 0.5 cm (suprasellar) or > 1 cm (pineal) but ≤ 1.5 cm residual) and second-look surgery is not performed, radiation therapy will follow and a higher dose to the ventricular volume will be administered with a subsequent increase in the total dose to the primary site. If

second-look surgery is not performed and patients do not meet criteria for at least PR with ≤ 1.5 cm residual disease, patients will be off protocol therapy.

15.2 Timing

15.2.1

It is recommended that all patients be seen in consultation by a radiation oncologist at the time of study enrollment. The purpose of the consultation is to participate in staging and to review the adequacy of the initial diagnostic imaging studies that will be used for subsequent RT planning.

15.2.2

There are no contraindications to radiation therapy. Patients taking phenytoin should be weaned and/or switched to a different anticonvulsant as soon as feasible.

15.2.3 Stratum 1 (NGGCT)

- If CR/PR after 6 cycles of induction chemotherapy, radiotherapy should commence within 3 weeks of recovery from last chemotherapy (Day 21) and no later than 6 weeks after the first day of the last chemotherapy cycle or the patient will be removed from protocol therapy (See Section 8.1).
- If PR, SD or PD after 6 cycles of induction chemotherapy, radiotherapy will not begin until after second-look surgery. Radiotherapy must begin within 31 days after surgery. If the patient has positive markers or <PR after second-look surgery, they will be removed from protocol therapy. If radiotherapy is not initiated within 31 days after surgery, the patient will be removed from protocol therapy.

15.2.4 Stratum 2 (Germinoma)

- If CR/CCR after 4 cycles of induction chemotherapy, low-dose radiotherapy should commence within 3 weeks of recovery from last chemotherapy (day 21) and no later than 6 weeks after the first day of the last chemotherapy cycle. If radiotherapy cannot be initiated by the above-mentioned time points, the patient will be removed from protocol therapy.
- If PR, SD, or PD after 4 cycles of induction chemotherapy, second surgery is highly recommended. If mature teratoma or non-viable tumor/fibrosis/scar is found, then low-dose radiotherapy will commence within 31 days after surgery. If the patient is found to have viable tumor other than mature teratoma, they will be removed from protocol therapy. If radiotherapy is not initiated within 31 days after surgery, the patient will be removed from protocol therapy.
- If PR or SD (> 0.5 cm suprasellar or > 1 cm pineal but ≤ 1.5 cm residual) after 4 cycles of induction chemotherapy and second surgery is not performed, moderate-dose radiotherapy will commence within 3 weeks of recovery from last chemotherapy and no later than 6 weeks after first day of the last chemotherapy cycle. If radiotherapy cannot be initiated by the above-mentioned time points, the patient will be removed from protocol therapy.

15.2.5

It is preferable to commence radiation treatments on or before a Thursday of any given week. Radiation is given 5 days a week, Monday through Friday.

15.3 Emergency Irradiation

Patients are not allowed to have received radiation therapy prior to enrollment on this protocol and urgent irradiation is not envisioned under any circumstance.

15.4 Equipment and Methods of Delivery and Verification

Equipment	Photons (any energy)	IMRT (4-10MV)	Protons
Linear Accelerator	X	X	
Proton Beam			X

15.4.1 Treatment planning

CT (volumetric) based planning is required to optimize dose to the PTV while protecting normal tissues. Organs at risk within the irradiated volume should be contoured including those required. A DVH is necessary to determine target coverage and evaluate dose to normal tissues. CT section thickness should be ≤3mm.

15.4.2 In-room verification of spatial positioning

15.4.2.1

Portal imaging is the most common system used to verify patient position, in particular when the target volume is believed to possess a fixed spatial relationship with visualized bony anatomy. If volumetric imaging is not available, orthogonal paired (AP and lateral) portal images (MV or kV) are required to verify that the isocenter is in correct alignment relative to the patient position. Beamline imaging of the treatment port should be performed when feasible. For proton treatment, orthogonal paired kV imaging for daily patient positioning and beamline kV imaging for treatment port verification are required.

15.4.2.2

Volumetric imaging is allowed in this study. This includes in-room kV or MV cone beam or conventional CT imaging. Please be able to submit representative axial images showing the isocenter and the correct alignment in relationship to the patients' position. For CT tomography where isocenters are not used, a printout of the isodoses overlaid on the fused CT images can be printed to demonstrate in room verification.

15.5 Target Volumes

15.5.1 General comments

International Commission on Radiation Units and Measurements (ICRU) Reports 50, 62 and 78 (www.icru.org) define prescription methods and nomenclature that will be utilized for this study. Although the MRI obtained immediately prior to

radiation therapy should be used for treatment planning, the target volumes for this study will be determined by the collective information that delineates the extent of disease before and after chemotherapy and second-look surgery. Patients require a combination of pre- and post-chemotherapy MR sequences to delineate the extent of disease and the ventricular volume. MR pre- and post-gadolinium contrast T1, T2, and FLAIR sequences should be reviewed. The sequences that best define the extent of initial disease and the post-chemotherapy ventricular volume should be registered to the treatment planning CT and used to determine the whole ventricular CTV and the local field boost GTV. The GTV, CTV and PTV and normal tissues must be outlined on all axial imaging slices on which the structures exist.

Practical Targeting Guidelines

After following the procedure outlined below, the investigator will have created and appropriately named six (n=6) target volumes: Whole Ventricular Volume (WVV), Whole Ventricular Volume CTV (WVVCTV), Whole Ventricular Volume PTV (WVVPTV), boost GTV (GTV), boost CTV (CTV) and boost PTV (PTV).

(1) Obtain a treatment planning CT using a ≤3mm image section thickness. Contrast is not required.
(2) Fuse the appropriate MR sequences
(3) Contour the GTV to satisfy the protocol requirement to delineate this volume.
(4) Expand GTV geometrically by 5mm to create a CTV for the boost phase of treatment.
(5) Expand the CTV geometrically by 3 or 5mm to create the PTV. Please note that a 3mm PTV margin expansion requires daily image guidance and intervention prior to treatment. A 5mm PTV margin expansion has no special requirements.
(6) Contour the WVV to satisfy the protocol requirement to delineate this volume.
(7) The WVV is not a volume representing gross tumor and therefore does not require a geometric expansion to form the WVVCTV. However, it is critical that the boost CTV be included in the WVVCTV to ensure the boost CTV receives the protocol specified dose. Add the boost CTV to the WVV. Please name this volume WVVCTV.
(8) Expand the WVVCTV geometrically by 3 or 5 mm to create the WVVPTV. Please note that that a 3mm PTV margin expansion requires daily image guidance and intervention prior to treatment. A 5mm PTV margin expansion has no special requirements.
(9) Please note that the boost volumes must be defined upfront to ensure this volume receives the protocol specified dose.

15.5.2 Photon definitions for whole ventricular volume, whole ventricular CTV and whole ventricular PTV

• A contouring atlas is available on the COG and IROC RI (QARC) websites (www.QARC.org).

- The whole ventricle volume (WVV) should encompass the lateral, third, and fourth Care should be taken to ensure the suprasellar and pineal cisterns are included in the whole ventricle volume. Inclusion of the prepontine cistern is optional but should be considered for patients that have undergone a third ventriculostomy and for patients with large suprasellar tumors. The whole ventricles should be contoured according to the whole ventricle atlas available on the COG website and QARC website. The fusion of T2 MR sequence obtained just prior to radiation therapy to assist in delineating CSF/ventricles is encouraged.

- Whole ventricular clinical target volume (WVVCTV):
  The whole ventricular volume represents an area of subclinical microscopic disease in the ventricular system and therefore a geometric margin is not required to form the WVVCTV. **However, it is critical that the WVV be combined with the boost CTV to ensure full dose to the involved field boost.** Combine the WVV and boost CTV to form the WVVCTV. The WVCTV should not extend outside of the bony calvarium.

- Whole ventricular planning target volume (WVVPTV):
  A geometric expansion of 3 or 5 mm should be added to the WVVCTV to create the WVVPTV. The PTV has two components, the internal margin (IM) and the set-up margin (SM). The IM is meant to compensate for all movements and variations in size and shape of the tissues contained within the WVVCTV. The SM is meant to account for set-up, mechanical and dosimetric uncertainties related to daily patient positioning, treatment equipment and software. Given that the WVVCTV is generally confined to the intracranial space, the WVVPTV may extend into or beyond bone but is unlikely to extend beyond the surface of the patient.

15.5.3 Photon definitions for boost volumes (GTV, CTV and PTV)

- Gross tumor volume (GTV) should include any residual tumor present at the time of treatment planning and all tissues initially involved or in contact with tumor prior to any intervention (surgery or chemotherapy). The GTV is defined as the tumor bed at the time of diagnosis accounting for shifts in normal tissues displaced by tumor that has responded to chemotherapy or has been removed by surgery. This does not apply to areas of parenchymal infiltration. Any region of the brain infiltrated by tumor should be included in the GTV.

  All diagnostic imaging should be reviewed prior to treatment planning and the sequences that best define the full extent of disease should be registered for treatment planning.

- Boost clinical target volume (CTV) includes the GTV with an added margin that is meant to treat subclinical microscopic disease and is anatomically

confined (i.e., the CTV is limited to the confines of the bony 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 5mm for all patients. When the GTV approaches the boundary of an anatomic compartment, the CTV will extend up to and include the boundary. The CTV margin chosen for this study requires diagnostic MR imaging data with image section thickness ≤ 5mm

- Boost planning target volume (PTV) includes a margin which is added to the CTV in 3-dimensions to create the PTV. It is geometric and not anatomically defined. The PTV has two components, the internal margin (IM) and the set-up margin (SM). The IM is meant to compensate for all movements and variations in size and shape of the tissues contained within the CTV. The SM is meant to account for set-up, mechanical and dosimetric uncertainties related to daily patient positioning, treatment equipment and software. For this study, the PTV margin should be 3 mm. Given that the CTV is generally confined to the intracranial space, the PTV may extend into or beyond bone but is unlikely to extend beyond the surface of the patient.

15.5.4 Proton definitions for GTV, CTV and PTV

- GTV is the same for protons and photons.
- CTV is the same for protons and photons.
- PTV will be uniquely defined for proton therapy (Section 15.6.4).
- When passive scattering or uniform scanning methods are used, the boost planning target volume (PTV) for proton therapy will include a margin which is added to the CTV in 3-dimensions. The margin should be consistent with the motion control and setup accuracy for the particular type of treatment at the treating proton center. **The PTV will be used for dose reporting and not specifically for treatment planning.** The goal of treatment planning will be CTV coverage at 100% directly with specific measures taken for each specific uncertainty, Specific adjustments will be made to (1) aperture margin definitions, (2) smearing of compensator, (3) range of the individual beams (depth of penetration), and (4) modulation width of the SOBP. The following parameters must be explicitly reported for each beam: range, modulation, smearing radius of the compensator, set-up margin (SM) and PTV margin. The specifics of dose reporting for the proton PTV and recommendations regarding the PTV margin are discussed in Section 15.6.4.

15.6 Target Dose

15.6.1 Dose Definition

Photon dose is to be specified in centigray (cGy)-to-muscle. For proton beam, the absorbed dose is specified in Gy (RBE), which is the same as ICRU 78 DRBE using a standard RBE of 1.10 with respect to water.

15.6.2 Prescribed dose and fractionation for NGGCT Stratum 1:

- The total dose to the whole ventricular PTV prescription isodose surface will be 3060 cGy administered in 17 fractions of 180cGy. The patient should be treated with one fraction per day. All fields should be treated each day for photon treatments. It is recommended that at least 2 fields be treated per day for proton treatments. Simultaneous integrated boost is not allowed.

The total dose to the boost PTV prescription isodose surface will be 2340 cGy administered in 13 fractions of 180cGy. The cumulative dose will be 5400 cGy. The patient should be treated with one fraction per day. All fields should be treated each day for photon treatments. It is recommended that at least 2 fields be treated per day for proton treatments. Simultaneous integrated boost is not allowed.

Table 15.6.2 Radiotherapy volume and dose guidelines for NGGCT Stratum 1*

Response	Whole Ventricle Dose	IF Boost Dose	Total Dose
CR/PR	3060cGy	2340cGy	5400cGy
CR/PR after second surgery	3060cGy	2340cGy	5400cGy
Mature teratoma/fibrosis/scar and CR/PR after second surgery	3060cGy	2340cGy	5400cGy
< PR after second surgery or positive markers	Off protocol therapy	Off protocol therapy	Off protocol therapy

* The dose per fraction is 180 cGy for both whole ventricle and boost dose

15.6.3 Prescribed dose and fractionation for Germinoma Stratum 2:

- The total dose to the whole ventricular PTV prescription isodose surface will be 1800 cGy administered in 12 fractions of 150cGy, unless the patient has had a PR to chemotherapy and has not undergone second-look surgery, in which case the whole ventricular PTV prescription isodose surface will be 2400 cGy administered in 16 fractions of 150cGy. The patient should be treated with one fraction per day. All fields should be treated each day for photon treatments. It is recommended that at least 2 fields be treated per day for proton treatments. Simultaneous integrated boost is not allowed.

- The total dose to the boost PTV prescription isodose surface will be 1200 cGy administered in 8 fractions of 150cGy. The cumulative dose will be 3000 cGy, unless the patient has had a PR to chemotherapy and has not undergone second-look surgery, in which case the cumulative dose will be

3600 cGy. The patient should be treated with one fraction per day. All fields should be treated each day for photon treatments. It is recommended that at least 2 fields be treated per day for proton treatments. Simultaneous integrated boost is not allowed.

Table 15.6.3 Radiotherapy volume and dose guidelines for Stratum 2*

Response	Whole Ventricle Dose	IF Boost Dose	Total dose
CR/CCR	1800cGy	1200cGy	3000cGy
PR (> 0.5 cm suprasellar or > 1 cm pineal but ≤ 1.5 cm residual disease and no Second-Look Surgery	2400cGy	1200cGy	3600cGy
Mature teratoma/fibrosis/scar found at Second-Look Surgery	1800cGy	1200cGy	3000cGy
Viable tumor found at second surgery or SD/PD > 1.5 cm and no Second-Look Surgery or positive markers	Off protocol therapy	Off protocol therapy	Off protocol therapy

*The dose per fraction is 150 cGy for both whole ventricle and boost dose.

15.6.4 Dose uniformity

For photons, at least 95% of the protocol-specified dose should encompass 100% of the whole ventricular PTV and the boost PTV and no more than 10% of either PTV should receive greater than 110% of the protocol dose as evaluated by DVH. The 100% isodose should be equal to the protocol specified dose. Wedges, compensators and other methods of generating more uniform dose distributions are encouraged.

For protons, treatment planning does not specifically use a PTV. All uncertainties are taken into account explicitly to create a robust plan that provides full dose coverage of the CTV. For passive scattering and uniform scanning, the aperture margin must include the appropriate beam penumbra for the selected beam energy, and setup and internal margins (SM and IM). These margins depend on the patient setup techniques used at the treating proton center. The aperture margin may be expanded further if a cold spot occurs near the edge of CTV due to insufficient lateral scatter. The smearing radius for the range compensator must be equal to the setup and internal margins (SM and IM). The beam range should be equal to the maximum water equivalent depth of the CTV plus a range margin. The main part of the range margin comes from uncertainty in CT accuracy and the conversion of the Hounsfield units to proton stopping power ratios. Most proton centers are expected to use 3.5% of the maximum water-equivalent depth of the CTV and then add another millimeter to account for uncertainties in beam range calibration and compensator fabrication. Additional range margin should be applied if internal motion could increase the water equivalent depth of the CTV. The modulation width should be increased consistently to ensure proximal coverage of the target volume. The beam range may be adjusted at the discretion of the treating radiation oncologist based on

normal tissue dose concerns. As noted in section 15.5.4, a PTV should be created by a uniform expansion from CTV for reporting purposes. The expansion margin should be consistent with SM and IM and is typically 3 mm for a static target volume when daily imaging is performed. With the planning guidelines provided herein, no more than 10% of PTV should receive greater than 110% of the protocol dose as evaluated by DVH. In most cases, at least 95% of the protocol-specified dose should encompass 100% of the PTV. A potential exception is when the range margin is smaller than the PTV expansion (e.g., 3mm). As a result, the beam may not penetrate deep enough to sufficiently cover the distal portion of the PTV. This may occur for shallow target volumes where the maximum depth of the CTV is small and the range margin is small. This scenario is not expected for this protocol; however, such incomplete coverage of the PTV will not constitute a planning deviation because the plan should be sufficiently robust to cover the CTV with the protocol specified dose accounting for all uncertainties.

15.6.5 Interruptions, Delays and Dose Modifications

There will be no planned rests or breaks from treatment, and once radiation therapy has been initiated, treatment will not be interrupted except for any life threatening infection or severe hematological toxicity defined as ANC < 300/μL or platelets less than 40,000/μL during the course of treatment. Blood product support should be instituted according to institutional/protocol guidelines. The reason for any interruptions greater than 3 treatment days should be recorded in the patient treatment chart and submitted with the QA documentation. There should be no modifications in dose fractionation due to age or field size. If one treatment is missed during a weekday, it may be made up on the weekend if the institutions allows. On weeks on which a holiday falls, radiation therapy may be given 4 days that week.

15.7 Treatment Technique

15.7.1 Beam Configuration

Every attempt should be made to minimize dose to organs at risk without compromising coverage of the target volume. Three-dimensional conformal therapy (coplanar or non-coplanar) or IMRT are required to minimize dose to normal tissues. Treatment techniques utilizing at least 3 fields are required and 5-7 fields are recommended. IMRT is recommended but not required.

15.7.2 Selection of proton beam arrangements

For protons, a 3-field technique employing 2 lateral fields and one PA field is recommended. Proton beams have two uncertainties at the distal edge of the beam that affect planning. The first is the physical uncertainty of the exact location of the stopping edge. This is accounted for in 15.6.4. The second is the biologic uncertainty of the distal range of the proton beam in which the RBE may be greater than 1.1; therefore, single proton beam plans which stop in a critical organ will not be allowed. Individual proton beams which are components of a multi-field proton beam and which stop within such an organ will be allowed but are not encouraged. It is preferable to stop the proton beam beyond the critical organ.

15.7.3 Field Shaping

Field shaping for photons will be done with either customized cerrobend blocking or multileaf collimation. Field shaping for protons will be done with either customized brass apertures, proton-specific multileaf collimation, or through scanning.

15.7.4 Simulation including patient positioning and immobilization

15.7.4.1 Patient positioning

Reproducible setups are critical and the use of immobilization devices is required. The patient should be treated in the supine position with arms at their sides. Consideration should be given to implications for inter and intrafraction motion when using non-standard position approaches.

15.7.4.2 Immobilization devices

Standard immobilization devices for the head are to be used. The methods used for localization and immobilization of both patient and tumor are critical. The imaging studies should provide a clear assessment of the target volume with the patient in the treatment position.

15.7.5 Special considerations

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

15.7.6 Motion Management and Margins to Account for Target Volume Changes During Treatment

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

- A margin matching the PTV margin may be added to any OAR to form the PRV.
- Any change in clinical condition or anatomy related to hydrocephalus, VP shunt placement, subdural fluid, pseudomeningocele or steroid use should be monitored carefully and with repeat imaging when indicated.

15.7.7 Treatment Planning Procedures

Table 15.7.7

Treatment Planning CT
Section thickness: ≤ 3mm
Volume: thoracic inlet-top of head
↓
Register MR Imaging
Pre-chemo (post-Gd T1WI)
Post-chemo (T2W1)
↓
Required Contours
WVV, WVVCTV, WVVPTV (15.5)
GTV, CTV, PTV (15.5)
Normal Tissue Contours (15.8)
↓
Radiation Treatment Planning
Target Volume Coverage (15.5)
Normal Tissue Dose Recommendations (15.8)
↓
Data Submission to QARC
Due Day 3 and End of Treatment (15.9)
Electronic and Hard Copy Data (15.9)

15.8 Organs at Risk

Planning should be done to minimize dose to the hypothalamus, pituitary, optic nerves, optic chiasm, retina, spinal cord, brainstem, and cochlea. Because the boost target volume may encompass the suprasellar region, it is possible that the hypothalamus, pituitary, optic chiasm and optic nerves may receive the total prescribed dose. No attempt should be made to spare these structures when they intersect or are adjacent to the target volumes. To avoid exceeding the suggested dose constraints, the dose coverage may be adjusted provided the guidelines of Section 15.6.4 are observed.

Following the recommendations of ICRU 62, a margin of 3-5 mm shall be added around each of these structures to compensate for geometric uncertainties. The volume, which includes this margin, is called the Planning Organ at Risk Volume (PRV). The dose to each of these PRV's shall not exceed 5400 cGy for Stratum 1. It is anticipated that lower doses to organs at risk can be obtained for Stratum 2. Sample drawings of these critical structures will be available on the IROC RI (QARC) website (www.QARC.org).

15.8.1 Optic Chiasm and optic nerves

The dose to the optic chiasm and optic nerves should not exceed 54 Gy and should be defined on CT or MR and appear on at least two successive images.

15.8.2 Cochlea

Each cochlea will be contoured on the CT data as a polygon or circular structure within the petrousportion of the temporal bone. The contour should appear on at least two successive CT images.

D50% < 3000cGy – Goal (single cochlea)
D50% < 2000cGy – Preferred (single cochlea)
Comment – There is no dose limit for the cochlea.

15.8.3 Brainstem

The dose to the spinal cord should not exceed 54 Gy.

15.8.4 Optic Globes

The dose to the optic globes should not exceed 45 Gy and a direct beam should be avoided.

15.8.5 Hypothalamus and Pituitary Gland

There is no dose constraint for the hypothalamus and pituitary gland. For primary tumors that do not involve the suprasellar region, field arrangements that minimize dose to these structures for the boost portion of the plan are encouraged.

15.9 Dose Calculations and Reporting

15.9.1 Prescribed Dose

The monitor units required to deliver the prescribed dose shall be calculated and submitted using the RT-1/IMRT Proton Dosimetry Summary Forms. If IMRT is used, 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 patient's plan can be directly applied to a phantom geometry. The daily and total prescribed dose shall be calculated and reported on the RT-2 Radiotherapy Total Dose Record. The dose should be prescribed to an isodose surface that encompasses the PTV and allows the dose uniformity requirements to be satisfied.

15.9.2 Normal Tissue Dosimetry

The dose to the critical organs indicated should be calculated whenever they are directly included in a radiation field. The total dose shall be calculated and reported on the RT-2 Radiotherapy Total Dose Record form. The appropriate dose-volume histograms should be submitted and RT-1 or IMRT form completed. If IMRT is used for the primary tumor, a DVH must be submitted for a category of tissue called "unspecified tissue," which is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure. A DVH for "Body" shall be submitted to enable calculation of the required volumes in Table 18.9b. "Body" is defined as the outer contour of the patient on the treatment planning CT data set.

Table 15.9a Required DVH data

Required DVH
Optic Chiasm
Brainstem
Spinal Cord
Right Cochlea
Left Cochlea
Hypothalamus
Pituitary Gland
Body
Unspecified Tissue

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

Table 15.9b Required Volumetric Information for Stratum 1

Required Volumes (ml)
TV95% = 51.3 Gy
TV100% = 54 Gy
IV35=V35Gy
IV45=V45Gy
IV54=V50Gy
WVV
WVVCTV
WVVPTV
GTV
CTV
PTV
Entire Brain
Unspecified Tissue

Table 15.9c Required Volumetric Information for Stratum 2, all patients except PR without second-look surgery

Required Volumes (ml)
TV95% = 28.5 Gy
TV100% = 30 Gy
IV15=V15Gy
IV20=V20Gy
IV25=V25Gy
WVV
WVVCTV
WVVPTV
GTV
CTV
PTV
Entire Brain
Unspecified Tissue

Table 15.9d Required Volumetric Information for Stratum 2, PR without second-look surgery

Required Volumes (ml)
TV95% = 34.2 Gy
TV100% = 36 Gy
IV15=V15Gy
IV20=V20Gy
IV30=V30Gy
WVV
WVVCTV
WVVPTV
GTV
CTV
PTV
Entire Brain
Unspecified Tissue

15.10 Quality Assurance Documentation

Digital Submission:
Submission of treatment plans in digital format (either DICOM RT or RTOG format) is required. Digital data must include CT scans, structures, plan, and dose files. Submission may be by either sFTP or CD. Instructions for data submission are on the QARC web site at www.qarc.org under "Digital Data." Any items on the list below that are not part of

the digital submission may be included with the transmission of the digital RT data via sFTP or submitted separately. Screen captures are preferred to hard copy for items that are not part of the digital plan.

15.10.1 On-treatment Review

Within three days of the start of radiotherapy, the following data for the whole ventricle fields shall be submitted for on-treatment review. Boost data must be submitted prior to the start of the boost, but preferably should be submitted with the whole ventricle data at the start of radiotherapy:

Treatment Planning System Output:

- RT treatment plans including CT, structures, dose, and plan files. These items are included in the digital plan.
- Dose volume histograms (DVH) for the composite treatment plan for all target volumes and required organs at risk. When using IMRT, a DVH shall be submitted for a category of tissue called "unspecified tissue." This is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure. DVHs are included in the digital plan.
- Digitally reconstructed radiographs (DRR) for each treatment field. Please include two sets, one with and one without overlays of the target volumes and organs at risk. When using IMRT, orthogonal setup images are sufficient.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.

Supportive Data:

- Copies of the operative reports for each surgical procedure.
- Copies of the prechemotherapy and postchemotherapy MRI scans and radiology reports utilized in defining the initial clinical target volume and the local boost volume.
- Pre-operative and post-operative cranial neuroimaging and radiology reports for each surgical procedure including second surgery after induction chemotherapy.
- Post-chemotherapy (pre-RT) neuroimaging and radiology reports when no second surgery was performed.
- Documentation of an independent check of the calculated dose when IMRT is used.
- If the recommended doses to the organs at risk are exceeded, an explanation should be included for review by the QARC and the radiation oncology reviewers.
- Proton therapy: smearing radius of the compensator, set-up margin (SM) and PTV margin for each treatment beam.

Forms:

- RT1/IMRT Dosimetry Summary Form (QARC).
- Proton Dosimetry Summary Form (QARC).

15.10.2 Post Treatment Review

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

- RT-2 Radiotherapy Total Dose Record Form.
- Radiotherapy record (treatment chart) including prescription and daily and cumulative doses to all required areas and organs at risk.

Electronic submission via sFTP for all data is preferred. Alternatively, the supportive data and forms may be sent to:

IROC RI (QARC)
640 George Washington Highway
Building B, Suite 201
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601

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

COG Protocol Dosimetrist
IROC RI (QARC)
640 George Washington Highway
Building B, Suite 201
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601

15.11 Definitions of Deviations in Protocol Performance

In the following table, the GTV, CTV and PTV descriptions and evaluations will applied and scored separately to the ventricular and boost phases of treatment.

	DEVIATION	
	Minor	**Major**
Prescription Dose		
	Difference in prescribed or computed dose is 6-10% of protocol specified dose	Difference in prescribed or computed dose is > 10% of protocol specified dose
Dose Uniformity		
	>10% PTV received > 110% of the prescription dose *or* 95% isodose covers < 100% of CTV	90% isodose covers < 100% of CTV
Volume		
	CTV or PTV margins are less than the protocol specified margins in the absence of anatomic barriers to tumor invasion (CTV) or without written justification (PTV)	GTV does not encompass MR-visible residual tumor
Organs at Risk		
	Dose to any OAR exceeds the goal dose stated in Section 15.8	Dose to any OAR exceeds the maximum dose stated in Section 15.8

Timing

Minor Deviation: Radiation therapy course prolonged 7-14 days.

Major Deviation: Radiation therapy course prolonged more than 14 days.

15.12 Patterns of Failure Evaluation

The patterns of failure for patients with localized CNS GCT may be described as local, ventricular, distant or a combination of local, ventricular, and/or 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. Ventricular failure is defined as the appearance of tumor at sites within the ventricular system other than known prior sites of disease. Distant failure is defined as the appearance of tumor at sites outside the ventricles or the primary tumor volume. Distant failure most often occurs in the subarachnoid space and may occur at any point within the neuraxis. Although rare, extra-CNS metastasis represents distant failure. Combined local, ventricular, and/or distant failure is defined when evaluation of the entire neuraxis reveals failure at two or three of the defined categories. 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.

There is no universally accepted analytical method to assess pattern of failure. 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.

16.0 NEUROPSYCHOLOGICAL FUNCTION STUDY

Note: Patients must be enrolled on ALTE07C1 at the time of study enrollment on ACNS1123.

A separate informed consent for ALTE07C1 must be signed. Please refer to the ALTE07C1 protocol for eligibility requirements.

Because of the high risk of neurodevelopmental problems in young children treated for CNS germ cell tumors, 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 sequelae for all children, including the very young. While it has historically been difficult to obtain neuropsychometric data in a cooperative group study, this is now feasible with ALTE07C1. These data are critical to the success of this treatment approach and its acceptance by patients, parents, and the neuro-oncology community.

APPENDIX I: CTEP AND CTSU REGISTRATION PROCEDURES

CTEP INVESTIGATOR REGISTRATION PROCEDURES

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

CTSU REGISTRATION PROCEDURES

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Requirements for ACNS1123 Site Registration:

- CTSU IRB Certification (for sites not participating via the CIRB)

- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

Submitting Regulatory Documents:

Submit completed forms along with a copy of your IRB Approval to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

APPENDIX II: POSSIBLE DRUG INTERACTIONS

The lists below do not include everything that may interact with chemotherapy. Study Subjects and/or their Parents should be encouraged to talk to their doctors before starting any new medications, using over-the-counter medicines, or herbal supplements and before making a significant change in diet.

Carboplatin

Drugs that may interact with carboplatin*
• Antibiotics like gentamicin or tobramycin • Anti-seizure medications like fosphenytoin or phenytoin • Arthritis medications like leflunomide, tofacitinib • Some chemotherapy (be sure to talk to your doctor about this) • Other medications like clozapine or natalizumab

Food and supplements that may interact with carboplatin**
• Echinacea

**Sometimes these drugs are used with carboplatin on purpose. Discuss all drugs with your doctor.*

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Etoposide

Drugs that may interact with etoposide*

• Antibiotics
  • Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin
• Antidepressants and antipsychotics
  • Aripiprazole, clozapine, nefazodone
• Antifungals
  • Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
• Arthritis medications
  • Leflunomide, tofacitinib
• Anti-rejection medications
  • Cyclosporine, tacrolimus
• Antiretrovirals and antivirals
  • Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir,

Stribild, telaprevir, tipranavir
• Anti-seizure medications
  • Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone
• Heart medications
  • Amiodarone, dronedenarone, verapamil
• Some chemotherapy (be sure to talk to your doctor about this)
• Many other drugs, including the following:
  • Aprepitant, atovaquone, bosentan, deferasirox, dexamethasone, ivacaftor, lomitapide, mifepristone, natalizumab, pimozide, sitaxentan

Food and supplements that may interact with etoposide**
• Echinacea • Glucosamine • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

**Sometimes these drugs are used with etoposide on purpose. Discuss all drugs with your doctor.*

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Ifosfamide

Drugs that may interact with ifosfamide*

• Antibiotics
  • Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin
• Antidepressants and antipsychotics
  • Citalopram, clozapine, escitalopram, fluvoxamine, lurasidone, nefazodone, paliperidone, quetiapine, thioridizine, ziprasidone
• Antifungals
  • Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
• Arthritis medications
  • Leflunomide, tofacitinib
• Anti-rejection medications
  • Cyclosporine
• Antiretrovirals and antivirals
  • Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir, tipranavir
• Anti-seizure medications
  • Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone
• Heart medications
  • Amiodarone, dronedenarone, verapamil
• Stomach and reflux medications
  • Esomeprazole, omeprazole

• Some chemotherapy (be sure to talk to your doctor about this) • Many other drugs, including the following: • Bosentan, sitaxentan, aprepitant, dexamethasone, lomitapide, mifepristone, natalizumab, pimozide

Food and supplements that may interact with ifosfamide**
• Echinacea • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

**Sometimes these drugs are used with ifosfamide on purpose. Discuss all drugs with your doctor.*

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

APPENDIX III: YOUTH INFORMATION SHEETS

INFORMATION SHEET REGARDING RESEARCH STUDY – ACNS1123
Non-Germinomatous Germ Cell Tumor (NGGCT)
(for children from 7 through 12 years of age)

Phase 2 Trial of Response-Based Radiation Therapy for Patients with Localized Central Nervous System Germ Cell Tumors

1. We have been talking with you about your non-germinomatous germ cell tumor (NGGCT). A NGGCT is a type of cancer that grows in your brain. Your tumor is localized meaning it has not spread to other areas of your brain, spinal canal or body. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study to see if localized NGGCT tumors treated with chemotherapy and radiation treatments with a smaller dose of radiation will work as well as radiation treatments used in previous studies. A research study is when doctors work together to try out new ways to help people who are sick. We will talk to you about enrolling on another COG study, ALTE07C1. The goal of ALTE07C1 is to learn about the thinking, learning, and remembering) of children being treated for cancer.

3. Standard treatment for NGGCT tumors includes chemotherapy to shrink the tumor as much as possible followed by radiation treatments. Radiation treatments used to treat NGGCT is usually given to the whole brain and is often given to the spinal column as well.

4. Children who are part of this study will be treated with chemotherapy called Induction chemotherapy followed by radiation treatments. The treatment on this study takes about 8 months. It is divided in to 2 stages. In the first stage, you will receive 6 cycles of induction chemotherapy. In the second stage, you may receive radiation treatments with a smaller dose. You may also have a second surgery before you receive radiation treatments.

5. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that the new treatments work better to get rid of the tumor than the standard treatment and causes less damage to your brain. But, we do not know for sure if there is any benefit of being part of this study.

6. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." One risk to you from this study is that the study treatment may not work as well as other treatments to make your tumor get smaller or go away for as long as possible. Other things may happen to you that we don't yet know about.

7. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

INFORMATION SHEET REGARDING RESEARCH STUDY – ACNS1123
Non-Germinomatous Germ Cell Tumor (NGGCT)
(for teens from 13 through 17 years of age)

Phase 2 Trial of Response-Based Radiation Therapy for Patients with Localized Central Nervous System Germ Cell Tumors

1. We have been talking with you about your non-germinomatous germ cell tumor (NGGCT). A NGGCT is a type of cancer that grows in your brain. Your tumor is localized meaning it has not spread to other areas of your brain, spinal canal or body. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study to see if localized NGGCT tumors treated with chemotherapy and radiation treatment with a smaller dose of radiation will work as well as radiation treatments used in previous studies. A research study is when doctors work together to try out new ways to help people who are sick. We will talk to you about enrolling on another COG study, ALTE07C1. The goal of ALTE07C1 is to learn about the thinking, learning, and remembering of children being treated for cancer.

3. Standard treatment for NGGCT tumors includes chemotherapy to shrink the tumor as much as possible followed by radiation treatments. Radiation treatments used to treat NGGCT is usually given to the whole brain and is often given to the spinal column as well.

4. Children who are part of this study will be treated with chemotherapy called Induction chemotherapy followed by radiation treatments. The treatment on this study takes about 8 months. It is divided in to 2 stages. In the first stage, you will receive 6 cycles of induction chemotherapy. In the second stage, you may receive radiation treatments with a smaller dose. You may also have a second surgery before you receive radiation treatment.

5. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that the new treatments work better to get rid of the tumor than the standard treatment and causes less damage to your brain. But, we do not know for sure if there is any benefit of being part of this study.

6. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." One risk to you from this study is that the study treatment may not work as well as other treatments to make your tumor get smaller or go away for as long as possible. Other things may happen to you that we don't yet know about.

7. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

INFORMATION SHEET REGARDING RESEARCH STUDY – ACNS1123
Germinoma Germ Cell Tumor
(for children from 7 through 12 years of age)

Phase 2 Trial of Response-Based Radiation Therapy for Patients with Localized Central Nervous System Germ Cell Tumors

1. We have been talking with you about your germinoma germ cell tumor. A germinoma tumor is a type of cancer that grows in your brain. Your tumor is localized meaning it has not spread to other areas of your brain, spinal canal or body. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study to see if localized germinoma tumors treated with chemotherapy and radiation treatments with a smaller dose of radiation will work as well as radiation treatments used in previous studies. A research study is when doctors work together to try out new ways to help people who are sick. We will talk to you about enrolling on another COG study, ALTE07C1. The goal of ALTE07C1 is to learn about the thinking, learning, and remembering of children being treated for cancer.

3. Standard treatment for germinoma tumors includes chemotherapy to shrink the tumor as much as possible followed by radiation treatments. Radiation treatments used to treat germinoma is usually given to the whole brain and is often given to the spinal column as well.

4. Children who are part of this study will be treated with chemotherapy called Induction chemotherapy followed by radiation treatment. The treatment on this study takes about 6 months. It is divided in to 2 stages. In the first stage, you will receive 4 cycles of induction chemotherapy. In the second stage, you may receive radiation treatments with a smaller dose. You may also have a second surgery before you receive radiation treatments.

5. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that the new treatments work better to get rid of the tumor than the standard treatment and causes less damage to your brain. But, we do not know for sure if there is any benefit of being part of this study.

6. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." One risk to you from this study is that the study treatment may not work as well as other treatments to make your tumor get smaller or go away for as long as possible. Other things may happen to you that we don't yet know about.

7. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

INFORMATION SHEET REGARDING RESEARCH STUDY – ACNS1123
Germinoma Germ Cell Tumor
(for teens from 13 through 17 years of age)

Phase 2 Trial of Response-Based Radiation Therapy for Patients with Localized Central Nervous System Germ Cell Tumors

1. We have been talking with you about your germinoma germ cell tumor. A germinoma tumor is a type of cancer that grows in your brain. Your tumor is localized meaning it has not spread to other areas of your brain, spinal canal or body. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study to see if localized germinoma tumors treated with chemotherapy and radiation treatment with a smaller dose of radiation will work as well as radiation treatments used in previous studies. A research study is when doctors work together to try out new ways to help people who are sick. We will talk to you about enrolling on another COG study, ALTE07C1. The goal of ALTE07C1 is to learn about the thinking, learning, and remembering of children being treated for cancer.

3. Standard treatment for germinoma tumors includes chemotherapy to shrink the tumor as much as possible followed by radiation treatments. Radiation treatments used to treat germinoma is usually given to the whole brain and is often given to the spinal column as well.

4. Children who are part of this study will be treated with chemotherapy called Induction chemotherapy followed by radiation treatment. The treatment on this study takes about 8 months. It is divided in to 2 stages. In the first stage, you will receive 4 cycles of induction chemotherapy. In the second stage, you may receive radiation treatment with a smaller dose. You may also have a second surgery before you receive radiation treatment.

5. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits." We hope that a benefit to you of being part of this study is that the new treatments work better to get rid of the tumor than the standard treatment and causes less damage to your brain. But, we do not know for sure if there is any benefit of being part of this study.

6. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks." One risk to you from this study is that the study treatment may not work as well as other treatments to make your tumor get smaller or go away for as long as possible. Other things may happen to you that we don't yet know about.

7. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

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