COG-ACNS0831
Phase III Randomized Trial of Post-Radiation Chemotherapy in Patients with Newly Diagnosed Ependymoma Ages 1 to 21 years

FAST FACTS
Eligibility Reviewed and Verified By
_____ MD/DO/RN/LPN/CRA Date _____
_____ MD/DO/RN/LPN/CRA Date _____
Consent Version Dated_____

PATIENT ELIGIBILITY:

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

___1. Patients must be enrolled on study within 56 days of initial surgical resection. Surgical resection is defined as any attempt to resect tumor that results in the tissue diagnosis of ependymoma (including biopsy). Patients must be enrolled before treatment begins.
The date protocol therapy is projected to start must be no later than 21 calendar days after the date of study enrollment.
Enrollment onto ALTE07C1 is strongly encouraged.

___2. Mandatory Submission of Imaging Studies for Central Review (See Section 17.0)
Pre-and post-operative brain and total spine MR with and without gadolinium must be submitted to the Quality Assurance Review Center (IROC RI (QARC)) to confirm eligibility.
Please note that there are other **required** Rapid Central Imaging Review time points for patients with a sub-total resection patients. For all imaging requirements with timing please see Section 17.1 and Section 17.6.

___3. Mandatory Submission of Tissue for Central Pathology Review (See Section 14.0)
All patients must have tissue submitted for central pathology review after study enrollment.
Patients with an infratentorial primary site must have pathology slides from the time of diagnosis submitted to the COG Biopathology Center within 10 days of study enrollment**.**

Patients with a supratentorial primary site must have RAPID CENTRAL PATHOLOGY REVIEW, in order to avoid discordant diagnoses and to verify diagnosis criterion for treatment stratification**. Pathology slides must be marked RAPID REVIEW and submitted by Federal Express Priority Overnight to the Biopathology Center within 5 days of study enrollment (See Section 14.0 for information regarding specimen submission). Results of rapid central review will be available within 1 week of the submission of pathology review materials.**

___4. Patients must be greater than 12 months of age and less than 21 years of age at the time of study enrollment.

___5. Patients must be newly diagnosed with histologically confirmed intracranial ependymoma. Patients with classic ependymoma (WHO II) or anaplastic ependymoma (WHO III) are eligible, as are various subtypes described as clear cell, papillary, cellular or a combination of the above.
Note: Please see imaging and pathology requirements in Section 3.1.6 and 3.1.7.

___6. Performance Level
There is no minimum performance level. Children with ependymoma may suffer neurologic sequelae as a result of their tumor or surgical measures taken to establish a diagnosis and resect the tumor. In the majority of cases there is neurologic recovery. Neurologic recovery is not likely to be impeded by protocol therapy.

EXCLUSION CRITERIA:

___1. Metastatic Disease
Patients with evidence of metastatic disease will be excluded. Any evidence of non-contiguous spread beyond the primary site as determined by pre or post-operative MR imaging of brain, pre or post-operative MR imaging of the spine, and post-operative CSF cytology obtained from the lumbar CSF space (the requirement for lumbar CSF examination may be waived if deemed to be medically contraindicated). CSF cytology from a ventriculostomy or permanent VP shunt that reveals the presence of tumor cells is indicative of metastatic disease.

___2. Ineligible Diagnoses
Patients with a diagnosis of spinal cord ependymoma, myxopapillary ependymoma, subependymoma, ependymoblastoma, or mixed glioma are NOT eligible.

___3. Prior Therapy
No prior treatment other than surgical intervention and corticosteroids. Patients are allowed to have had more than one attempt at resection prior to enrollment.

___4. Pregnant female patients are not eligible for this study.

___5. Post-menarchal females may not participate unless a pregnancy test with a negative result has been obtained.

___6. Males and females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method.

___7. Lactating females may not participate unless they have agreed not to breastfeed a child while on this study.

Assignment to Treatment Arms and Randomization
Patients will be randomized or non-randomly assigned to treatment arms based upon 1) the extent of resection, 2) tumor histology and 3) tumor location.

Randomization
For patients eligible for randomization after initial surgery, randomization should occur as soon as possible after enrollment using the Callback function of the Member Site. Patients must be randomized **prior** to radiation. Patients who will receive proton therapy are eligible for this study. Definitions for extent of surgical resection can be found in Section 4.1.

Supratentorial Patients
Patients with **classic histology supratentorial disease** who have GTR1 after initial surgery will be non-randomly assigned to observation only. Rapid central pathology review will be performed on all supratentorial tumors to confirm eligibility for observation only after enrollment. See Section 14.2.1for discordant diagnosis.

Supratentorial patients with 1) GTR2 or 2) NTR, and with 3) anaplastic histology or 4) indeterminate grade histology will be randomized.

Note: Treatment or randomization for supratentorial patients cannot be started until the central pathology review results are available.

Infratentorial Patients
Patients with an infratentorial primary tumor that have a total or near total resection ([GTR1 or GTR2 or NTR] definitions in Section 4.1) regardless of histology will be randomized.

STR (Incomplete Resection) Patients
Patients with a subtotal resection (STR) (definition in Section 4.1) after initial surgery will be non-randomly assigned to induction chemotherapy. Induction chemotherapy consists of 7 weeks (2 cycles) of chemotherapy. At the end of induction, patients must have rapid central imaging review to confirm response to therapy and determine the next steps.

Patients with a Complete Response following Induction:
Supratentorial Classic Histology: patients with a classic histology supratentorial tumor that have a CR following induction chemotherapy will be non-randomly assigned to observation.

Infratentorial with Any Histology and Supratentorial Anaplastic Histology: Those who have a CR (see definition in Section 10.0) following induction chemotherapy and have either an infratentorial primary or a supratentorial anaplastic primary tumor will be randomized.

Patients with Stable Disease, Partial Responses, Progressive Disease following Induction:
Patients with stable disease (SD), partial response (PR) or locally progressive disease (LPD) (see definitions in Section 10.4) after induction chemotherapy will undergo second surgery when possible. There is no limit to the number of surgical procedures performed after induction chemotherapy and prior to cRT.

Following Second Surgery
Patients with an infratentorial primary or supratentorial anaplastic primary tumor who have a GTR1, GTR2 or NTR after second surgery will then be randomized.

Patients with residual disease after second surgery will be non-randomly assigned to receive cRT followed by maintenance chemotherapy.

Patients with supratentorial classic primary tumor who have a GTR1 after second surgery will be assigned to observation only.

Detailed information about the Treatment Plan including randomization at diagnosis and following induction chemotherapy and/or second surgery can be found in Section 4.0.

Required Clinical, Laboratory and Disease Evaluations for STR (Incomplete Resection) Patients

Studies to be Obtained at Study Entry
- History, Physical Exam, Weight and Height
- MR Brain with gadolinium [2]
- MR Spine with gadolinium [3]
- Lumbar CSF Cytology [1]
- Required Pathology Specimens (See Section 14.0)
- Ophthalmology Evaluation [5]
- Pregnancy Test [4]

1. Obtain unless lumbar puncture is contraindicated and deemed medically unsafe.
2. Obtain both pre and post-surgery. Post-op should be done within 72 hours. When the post-operative scan obtained within 72 hours is difficult to interpret, the scan should be repeated 10 or more days after surgery.
3. Obtain within 10 days prior to surgery or attempt to wait 10 days after surgery; should be performed with gadolinium.
4. Obtain for females of childbearing potential.
5. Prior to study enrollment is preferred although within 4 months of beginning RT is acceptable.

Studies to be Obtained Prior to Induction
- Neurologic Assessment
- Electrolytes (including Ca++, PO4, Mg++, BUN)
- Serum Creatinine or GFR or Creatinine Clearance
- Liver Function (ALT, AST, Total Bili)
- Urinalysis
- CBC (w/Differential and Platelets)
- Audiogram or BAER

Required Clinical, Laboratory and Disease Evaluations for Patients Randomized to Radiation Therapy followed by Maintenance Chemotherapy

Studies to be Obtained at Study Entry

- History, Physical Exam, Weight and Height
- MR Brain with gadolinium [2]
- MR Spine with gadolinium [3]
- Lumbar CSF Cytology [1]
- Required Pathology Specimens (See Section 14.0)
- Ophthalmology Evaluation [5]
- Pregnancy Test [4]

1. Obtain unless lumbar puncture is contraindicated and deemed medically unsafe.
2. Obtain both pre and post-surgery. Post-op should be done within 72 hours. When the post-operative scan obtained within 72 hours is difficult to interpret, the scan should be repeated 10 or more days after surgery.
3. Obtain within 10 days prior to surgery or attempt to wait 10 days after surgery; should be performed with contrast.
4. Obtain for females of childbearing potential.
5. Prior to study enrollment is preferred although within 4 months of beginning RT is acceptable.

Studies to be Obtained Prior to cRT

- History, Physical Exam, Weight and Height
- Neurologic Assessment
- MR Brain with gadolinium [2]
- CBC (w/Differential and Platelets)
- Audiogram or BAER
- Ophthalmology Evaluation [3]
- Endocrine Evaluation [1]

1. Endocrine evaluation to include: TSH/free T4 or alternative and growth hormone. Tanner Stage (See Appendix III) and LH/FSH and Estradiol/testosterone if child has delay puberty or precocious puberty before age 8 in girls or 9 in boys beginning at age 11 or with signs of precocious puberty. Cortisol (8 am) - begin screening at age 11 or with signs of precocious puberty.
2. Preferably the scan should be performed within 21 days of beginning radiation and MUST be performed within 28 days of beginning RT. (Post-op imaging can be used).
3. Prior to study enrollment is preferred although within 4 months of beginning RT is acceptable.

Required Clinical, Laboratory and Disease Evaluations for Patients Randomized to Receive Radiation Therapy followed by Observation

Studies to be Obtained at Study Entry

- History, Physical Exam, Weight and Height
- MR Brain with gadolinium [2]
- MR Spine with gadolinium [3]
- Lumbar CSF Cytology [1]
- Required Pathology Specimens (See Section 14.0)
- Ophthalmology Evaluation [5]
- Pregnancy Test [4]

1. Obtain unless lumbar puncture is contraindicated and deemed medically unsafe.
2. Obtain both pre and post-surgery. Post-op should be done within 72 hours. When the post-operative scan obtained within 72 hours is difficult to interpret, the scan should be repeated 10 or more days after surgery.
3. Obtain within 10 days prior to surgery or attempt to wait 10 days after surgery; should be performed with contrast.
4. Obtain for females of childbearing potential.
5. Prior to study enrollment is preferred although within 4 months of beginning RT is acceptable.

Studies to be Obtained Prior to cRT

- History, Physical Exam , Weight and Height
- Neurologic Assessment
- MR Brain with gadolinium [2]
- CBC (w/Differential and Platelets)
- Audiogram or BAER
- Ophthalmology Evaluation [3]
- Endocrine Evaluation [1]

1. Endocrine evaluation to include: TSH/free T4 or alternative and growth hormone. Tanner Stage (See Appendix III) and LH/FSH and Estradiol/testosterone if child has delay puberty or precocious puberty before age 8 in girls or 9 in boys beginning at age 11 or with signs of precocious puberty. Cortisol (8 am) - begin screening at age 11 or with signs of precocious puberty.
2. Preferably the scan should be performed within 21 days of beginning radiation and MUST be performed within 28 days of beginning RT. (Post-op imaging can be used).
3. Prior to study enrollment is preferred although within 4 months of beginning RT is acceptable.

Required Observations For Supratentorial Classic Ependymoma GTR1 Patients (Observation)
Observation (Time measured from date of enrollment)

- History and Physical
- Height, Weight
- Neurologic Assessment
- MR Brain with gadolinium
- MR Spine (with gadolinium) [1]
- CSF Cytology [2]
- Audiogram or BAER
- Ophthalmology Evaluation
- Endocrine Evaluation [3]
- Required Pathology Specimens (See Section 14.0)

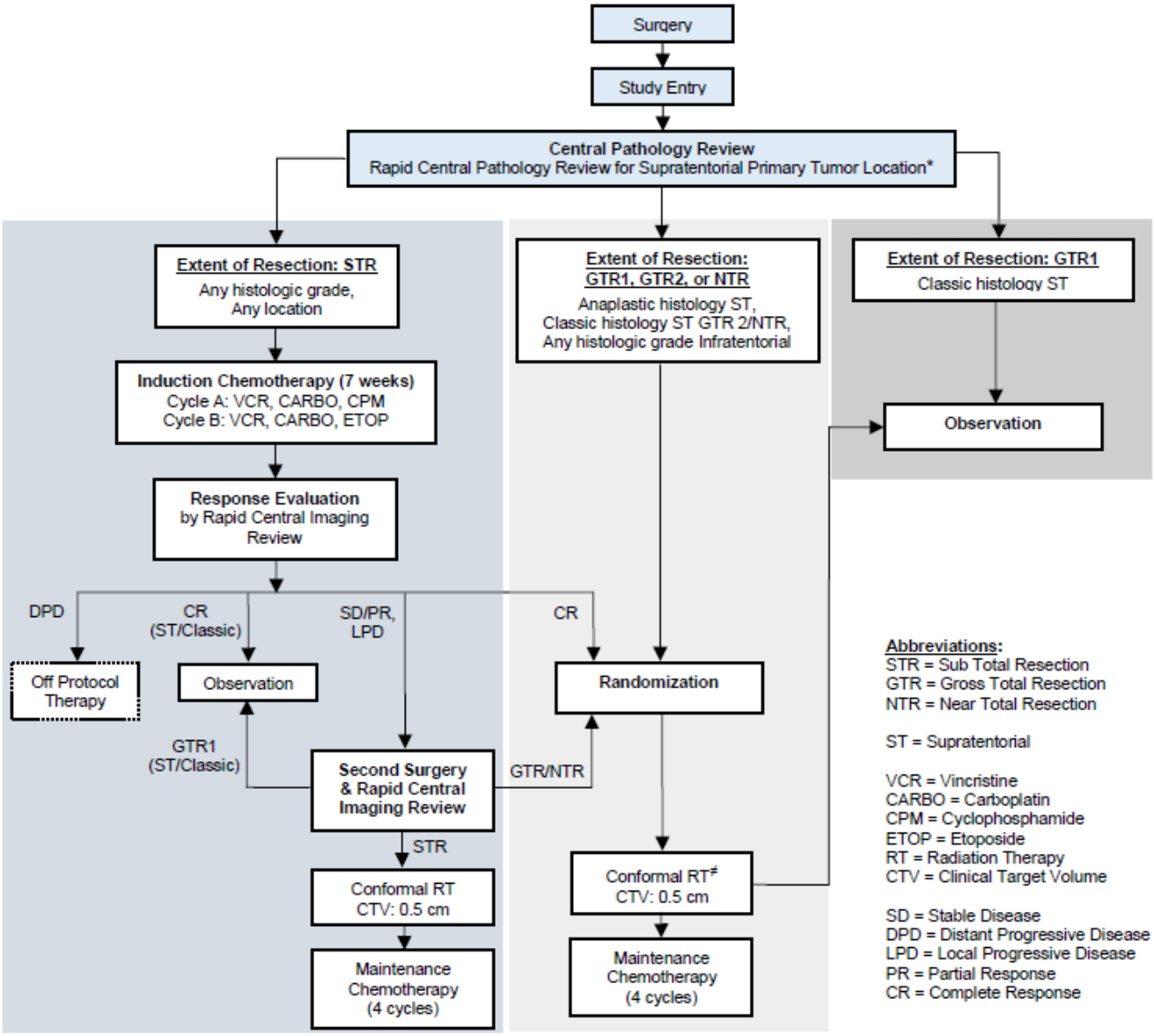
1. Repeat if new symptoms develop or if patient has local recurrence.
2. Obtain unless lumber puncture is contraindicated and deemed medically unsafe. Must be negative at baseline, otherwise patients is excluded.
3. Endocrine evaluation to include: TSH/free T4 or alternative and growth hormone. Tanner Stage (See Appendix III) and LH/FSH and Estradiol/testosterone if child has delayed puberty or precocious puberty before age 8 in girls or 9 in boys beginning at age 11 or with signs of precocious puberty. Cortisol (8 am) - begin screening at age 11 or with signs of precocious puberty.

TOXICITIES AND DOSAGE MODIFICATIONS:
See Section 5.0

SPECIMEN REQUIREMENTS:
Central Pathology Review required for all patient.
Rapid Central Pathology Review required for patients with Supratentorial Primary Tumors
Also see Section 14

BIOLOGY REQUIREMENTS:
See Section 7.5.1 and Section 15 for Optional Biology Studies

TREATMENT PLAN:



* Rapid Central Pathology Review will be performed on All Supratentorial Patients. Please see Section 14.2.1 for details.

Guidelines for extent of resection can be found in Section 4.1.

- All patients with a sub total resection (STR), regardless of tumor location and histology, will receive **Induction**.
- All patients with an infratentorial tumor GTR 1, GTR 2, or NTR will be **Randomized**.
- All other GTR 1, GTR 2, and near total resection (NTR) supratentorial patients will be **Randomized**.
- Only Supratentorial patients who have classic histology confirmed by Rapid Central Pathology Review and gross total resection 1 (GTR 1) will be assigned to **Observation**.

≠ Under the condition that the extent of resection is indeterminate because the surgeon cannot unequivocally report that microscopic disease is not present OR the information necessary to determine extent of resection at the time of the operation is not available, the patient will be randomized (a) conformal radiation therapy (cRT) and maintenance chemotherapy OR (b) conformal radiation therapy (cRT) and observation.

Also see Section 4