1. STUDY TITLE: Outcomes of Adult Survivors of Childhood Astrocytoma and Ependymoma Across Three Decades of Diagnosis and Treatment, A Report from the Childhood Cancer Survivor Study

2. WORKING GROUP AND INVESTIGATORS
   2.1 Primary Working Group: Chronic Disease
   2.2 Secondary Working Group: Secondary Malignancy,
                                            Psychology/Neuropsychology
                                            Epidemiology/Biostatistics
                                            Cancer Control

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3. BACKGROUND AND RATIONALE

Low-grade astrocytomas and ependymomas make up more than a third of childhood brain tumors diagnosed annually in the United States,[1] and more than 70% of these pediatric patients become long-term survivors.[2, 3] Survivors of childhood brain tumors are at high risk for developing a variety of chronic health conditions (CHCs) years after their original treatment. Depending primarily on tumor location, morbidities from astrocytomas and ependymomas and their treatment include subsequent neoplasms, endocrine conditions and neurologic conditions.[4] The most common subsequent neoplasms identified include CNS tumors (both high-grade astrocytomas and meningiomas), soft tissue sarcomas and thyroid cancers.[4] Specific neurologic conditions include motor/coordination deficits, paralysis, sensory deficits/blindness/hearing loss, seizures, headaches and cognitive impairment. [5-7] Also, the cumulative incidence of subsequent neoplasms and new-onset neurologic conditions continue to increase across the lifespan.[7]

Importantly, a recent report from the Childhood Cancer Survivor Study (CCSS) cohort demonstrated an improvement in all-cause late mortality among survivors of childhood

astrocytoma from 1970 - 1999.[8] Specifically, adult survivors of childhood astrocytoma experienced a reduction in the cumulative incidence of death 15 years after diagnosis from 13.5% to 7.4% during this time period (p < 0.001). Among the astrocytoma survivors, there was no significant change in rate of death due to tumor recurrence or progression (p = 0.08), but there were decreases in death rates attributed to subsequent neoplasms (p = 0.02) and cardiac causes (p = 0.02), but not pulmonary causes (p = 0.72) and other causes (p = 0.84).[8] The treatment-related cause of this reduction in late mortality among astrocytoma survivors was not clear and was not explained by changes in a simplified therapy model (investigating the presence or absence of chemotherapy and radiation). Also, in this study, changes in late mortality among survivors of ependymoma were not investigated. A more detailed model of evolving treatments and psychosocial support for survivors of childhood astrocytomas and ependymomas may explain differences in all-cause late mortality and may be responsible for changes in morbidity over the decades.

Over the past decades, the evolution of adjuvant treatment for astrocytomas has attempted to mitigate late effects of therapy. Radiation therapy has been used for decades for the treatment of astrocytoma and offers excellent progression free survival. However, adult survivors of childhood brain tumors exposed to radiation suffer substantial chronic health conditions, especially when exposed at a young age.[4] In an effort to reduce many late effects and cognitive impairments, chemotherapy regimens were introduced to control the tumor and delay or avoid radiation therapy in developing children.[9] As the number of available chemotherapy regimens for low grade astrocytoma has expanded, studies examined whether regimens that reduced exposure to alkylating agents could have similar efficacy. Delays in radiation therapy, along with a reduction in alkylator exposure, may result in improved late effects among adult survivors of astrocytoma and may explain improvements seen in late mortality.

For childhood ependymoma, radiation therapy has remained a mainstay of therapy following maximal surgical resection. While various chemotherapy regimens have attempted to augment or replace radiation therapy in children with ependymoma, none have prolonged overall survival.[10, 11] However, advances in imaging and delivery of radiation have helped to reduce the volume of healthy tissue exposed, and radiation therapy for non-metastatic ependymoma has moved from whole brain radiation to more focal therapy.[12] Therefore, changes in the volume of healthy tissue exposed to radiation therapy may explain differences in late effects among adult survivors of childhood ependymoma.

Over three decades, changes in exposure to therapies may not be the only factor determining late effects in pediatric astrocytoma and ependymoma. Better recognition and support of psychosocial stressors in survivors over time may improve morbidity and mortality by reducing isolation and improving medical resources. For instance, improved function (including reduced psychological or cognitive impairments) and social attainment (including employment and health insurance status) outcomes may support better surveillance and treatment of late effects before they cause significant morbidity.

This project will explore the changes in mortality and late outcomes in adult survivors of childhood astrocytoma and ependymoma and investigate potential factors that may mediate the effect of treatment era on survival outcomes. Because pediatric astrocytomas and ependymomas underwent different evolutions of treatment during this period, these tumor types will be considered separately.

Many survivors of childhood astrocytoma and ependymoma have now reached an age where they are managing their chronic health conditions, engaging in intimate relationships and preparing for the future. It is important to evaluate the impact of late effects in this population given that we can now analyze outcomes from survivors from three decades of evolving care.

4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES
  4.1 Astrocytoma Aims
    4.1.1 Primary Aims and Hypothesis (Astrocytoma):
    4.1.1.1 Examine the change in all-cause and cause-specific late mortality in survivors of astrocytoma and compare by: 1) treatment era (1970-1979, 1980-1989, 1990-1999); and 2) changes in use of treatment modalities (radiation dose, time from diagnosis to first radiation, selective chemotherapeutic agents).

    4.1.1.2 Hypothesis: Standardized mortality ratios (SMRs) in survivors of childhood astrocytoma will decrease with later treatment era, and this effect will be mediated by changes in treatment that avoid/delay radiation and decrease alkylator exposure.
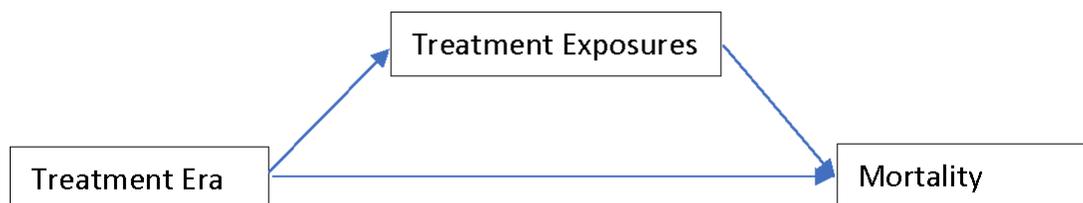
    4.1.2 Secondary Aims and Hypotheses (Astrocytoma):
    4.1.2.1 Determine the cumulative incidence and standardized incidence rates (SIRs) of all subsequent neoplasms (SNs) and of subsets of SNs including subsequent malignant neoplasms (SMNs) and benign meningiomas among survivors of astrocytoma and compare by: 1) treatment era (1970-1979, 1980-1989, 1990-1999); and 2) changes in treatment modality (radiation, chemotherapy).

    4.1.2.2 Hypothesis: The risk of subsequent neoplasm will be greatest in astrocytoma survivors treated with earlier/higher doses of radiation and higher alkylator chemotherapy.

4.1.2.3 Measure the occurrence and severity of chronic health conditions among survivors of astrocytoma and compare by: 1) treatment era (1970-1979, 1980-1989, 1990-1999); 2) changes in treatment modality (radiation, chemotherapy), and 3) levels of attainment and symptom indexes. Note: comparison of CHC to levels of attainment and symptom indexes will consider only CHCs that occur after baseline survey; other analyses will include all recorded CHCs.

4.1.2.4 Hypothesis: The risk and severity of chronic health conditions among survivors of childhood astrocytoma will be greatest in those treated in earlier treatment eras and those treated with earlier/higher doses of radiation and with increased alkylator therapy, as well as worse psychosocial symptom/attainment indexes.

4.1.2.5 Evaluate psychosocial outcomes, including Attainment (marriage, employment, insurance, and educational level) and Symptom (emotional distress, learning problems, pain, and social dysfunction) indexes for astrocytoma survivors in a path analysis involving: 1) treatment era (1970-1979, 1980-1989, 1990-1999); and 2) changes in treatment modality (radiation, chemotherapy)

4.1.2.6 Hypothesis: Survivors of astrocytoma who were treated in later treatment eras and those able to avoid or delay radiation therapy will have better Attainment (marriage, employment, insurance, and educational level) and Symptom (emotional distress, learning probems, pain, and social dysfunction) indexes compared to patients treated in earlier eras and those treated with higher/earlier radiation doses. A path analysis will demonstrate that psychosocial outcomes mediate the effect of treatment era on mortality.

4.2 Ependymoma aims
  4.2.1 Primary Aim and Hypothesis (Ependymoma)
  4.2.1.1 Examine the change in all-cause and cause-specific late mortality in survivors of ependymoma, and compare by: 1) treatment era (1970-1979, 1980-1989, 1990-1999); 2) changes in use of treatment modalities (radiation dose, field and time from diagnosis of radiation, selective chemotherapeutic agents); and 3) changes in attainment and symptom indexes

  Hypothesis: Standardized mortality ratios in survivors of childhood ependymoma will decrease with later treatment era, and this effect will be mediated by changes in treatment that decreased radiation field (whole brain vs focal radiation) and decrease chemotherapy exposure as well as improved psychosocial symptom/attainment indexes. (see path model below)

  4.2.2 Secondary Aims and Hypotheses (Ependymoma)
  4.2.2.1 Determine the cumulative incidence and standardized incidence rates (SIRs) of all subsequent neoplasms (SNs) and of subsets of SNs including subsequent malignant neoplasms (SMNs) and benign meningiomas among survivors of

ependymoma and compare by: 1) treatment era (1970-1979, 1980-1989, 1990-1999); and 2) changes in treatment modality (radiation, chemotherapy)

Hypothesis: The risk of subsequent neoplasm will be greatest in ependymoma survivors treated with higher doses/larger fields of radiation and more cumulative chemotherapy.

4.2.2.2 Measure the occurrence and severity of chronic health conditions among survivors of ependymoma and compare by: 1) treatment era (1970-1979, 1980-1989, 1990-1999); 2) changes in treatment modality (radiation, chemotherapy), and 3) changes in attainment and symptom indexes.

Hypothesis: The risk and severity of chronic health conditions among survivors of childhood ependymoma will be greatest in those treated in earlier treatment eras and those treated with larger fields of radiation (whole brain vs. focal radiation) and with increased chemotherapy exposure, as well as worse psychosocial symptom/attainment indexes. Note: comparison of CHC to levels of attainment and symptom indexes will consider only CHCs that occur after baseline survey; other analyses will include all recorded CHCs.

4.2.2.3 Evaluate psychosocial outcomes, including Attainment (marriage, employment, insurance, and educational level) and Symptom (emotional distress, learning problems, pain, and social dysfunction) indexes for ependymoma survivors in a path analysis involving: 1) treatment era (1970-1979, 1980-1989, 1990-1999); and 2) changes in treatment modality (radiation, chemotherapy). A path analysis will demonstrate that psychosocial outcomes mediate the effect of treatment era on mortality.

Hypothesis: Survivors of ependymoma who were treated in later treatment eras and those able to be treated with a lower dose/field of radiation therapy will have higher Attainment (marriage, employment, insurance, and educational level) and Symptom (emotional distress, learning problems, pain, and social dysfunction) indexes compared to patients treated in earlier eras and those treated with radiation of higher dose/larger fields. . A path analysis will demonstrate that psychosocial outcomes mediate the effect of treatment era on mortality.

5. ANALYSIS FRAMEWORK

   5.1 Outcome of interest
    5.1.1 Mortality (Aims 4.1.1.1 and 4.2.1.1)
     Vital status (alive/dead)
     All-Cause mortality
     Cause-specific mortality, including
          1) Recurrence or progression of primary childhood malignancy

2) External causes (accidents, injuries, suicide)
3) Other health-related causes
   a. Subsequent neoplasm
   b. Cardiac
   c. Pulmonary
   d. Other

5.1.2 Subsequent neoplasm (Aims 4.1.2.1 and 4.2.2.1)
   1) subsequent neoplasm (including both benign and malignant)
   2) subsequent malignant neoplasm, subcategorized by type (Tables 4 and 5)

5.1.3 Chronic health conditions (CHC) (Aims 4.1.2.2 and 4.2.2.2)
   1) Overall CHC: Using CTCAE grading, survivors will be classified as having:
      a) no CHC
      b) any grade 1-5 CHC
      c) any grade 3-5 CHC
      d) >1 grade 3-5 CHC

   2) Specific CHC: Any grade 3-5 CHC in the following categories will be evaluated
      a) endocrine (hyper or hypo-thyroidism requiring medication, GH deficiency requiring medication)
      b) cardiac
      c) pulmonary
      d) neurological (neurosensory deficits, focal neurologic dysfunction, seizures, stroke, headache as per concept 07-03)
      e) speech

5.1.5 Psychosocial outcomes (Aims 4.1.2.5 and 4.2.2.5)
5.1.5.1 Attainment index: The following variables that make up the psychosocial attainment index will be reported individually as outcome variables from the baseline surveys of the original and expansion cohorts:
   1) Marital Status (married/unmarried) B L1, <18 B L1, E M2, <18E M2
   2) Employment status (employed/unemployed) B O5, <18 B O6, E S1, <18 E
   3) Insurance status (insured/uninsured) B Q2, <18 B Q2, E U2, <18 E U2
   4) Education level (>college/not including college, based on baseline questionnaire) B O1, <18 B 01, E R1, <18 E R1
   5) Income level (>$20,000/<$20,000, based on baseline questionnaire) B Q9, <18 B Q8, E T3, <18 E T1
In addition, the composite psychosocial attainment index score (see section 5.3.5) will be reported as an outcome. Abnormal psychosocial attainment score will be the lowest (worst) tercile of the composite score.

5.1.5.2 Symptom Index: The following variables that make up the psychosocial symptom index will be reported individually and as composite outcome variables.

Outcomes are derived from the baseline surveys of the original and expansion cohorts::

1) Emotional distress: BSI-18 Global Distress Index $\geq$ 63 or two subscales $\geq$ 63 (depression, anxiety or somatization). B J16-25, 26, 27, 29-35; 2003 G1-18, E K1-18

2) Learning/Concentrating difficulty: "Yes" to the question of whether respondant was in a "Learning disabled or special education program" due to "problems learning or concentrating". Question 03c (original) R3c (expansion)

3) Pain: "Yes, and still present" to any question of pain including migraine (J6 original, J3 expansion), other headache (J7 original, J4 expansion), prolonged pain (J13 original, J9 expansion), chest pain in the last 7days (J18 original, K3 expansion), or cancer pain ("a lot" or "excruciating", J36 original, K19 expansion).

4) Social dysfunction: "quite a bit" or "extremely" to the question "Feeling lonely" in the past 7 days (original J21, expansion K6)

In addition, the composite psychosocial symptom index score (see section 5.3.3) will be reported as an outcome. Abnormal psychosocial symptom score will be the lowest (worst) tercile of the composite score.

5.2 Population of interest

Two patient populations will be used for this project. These will include: 1) all patients with a primary cancer diagnosis of astrocytoma in the CCSS cohort, and 2) all patients with a primary cancer diagnosis of ependymoma in the CCSS cohort. For Aim 1 mortality analyses, all eligible subjects will be used. For subsequent Aims, the subset of those who completed a baseline survey or, in the case of NCQ variables, the FU2 (2003) or FU5 surveys will be used.

5.3 Explanatory variables

5.3.1 Specific treatment exposures:

5.3.1.1 Astrocytoma treatment exposures

5.3.1.1.1 Chemotherapy exposure (Astrocytoma)
-Alkylating Agent (using cyclophosphamide equivalent dose)
-Cisplatin, cumulative dose
-Carboplatin, cumulative dose

5.3.1.1.2 Radiation exposure (Astrocytoma)
-Radiation exposure: yes; no
-Maximum tumor dose: none, <30Gy; 30–39.9 Gy; $\geq$40 Gy
-age at radiation
-delay in radiation from diagnosis (continuous variable: calculated as date of radiation – date of diagnosis, and as a categorical variable based on descriptive demographics of the cohort)

5.3.1.2 Ependymoma treatment exposures:

5.3.1.2.1 Chemotherapy exposure (Ependymoma)
-any chemo exposure: yes/no
-Alkylating Agent (using cyclophosphamide equivalent dose)

5.3.1.2.2 Radiation exposure (Ependymoma)
-Radiation exposure: yes; no
-Maximum tumor dose: none, <30 Gy; 30–39.9 Gy; $\geq$40 Gy
-Focal vs whole brain radiation. To define these terms, radiation exposure in the 4 brain segments will be examined in the cohort and a threshold of radiation exposure in each segment will be determined from examining a histogram of max therapeutic dose in each segment for the radiated cohort. Whole brain radiation will be defined as patients with a max therapeutic dose above the threshold (or above >20 Gy if no clear threshold exists) in all four brain segments. Focal radiation will be defined patients who received radiation (>20 Gy or similar threshold) in at least 1 segment but not in all 4 segments.
-age at radiation
-delay in radiation from diagnosis (continuous variable calculated as date of radiation – date of diagnosis)

5.3.2 Demographic characteristics:
-Age at diagnosis (<5 years, 5-9.9 years, 10-14.9 years, $\geq$15 years)
-Age at most recent contact (<20 years; 20 – 29.0 years; 30 – 39.9 years; $\geq$40 years)
-Race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic/Latino, Other) B A4, A4.a, <18 B A4, A4.a, E A5, A5.a, <18 E A5, A5.a
-Sex (M/F) B A2, <18 B A2, E A2, <18 E A2
-Neurofibromatosis type 1 (NF1) status (defined as in concept proposals 16-19 and 16-10)

5.3.3 Psychosocial indexes
Psychosocial symptom index and psychosocial attainment index will be calculated for each patient by summing the number of component measures for which they had impairment, with a maximum symptom score of 4 for symptom and 5 for attainment. In a multivariable model in this cohort, the association of variables from each index (section 5.1.5) on cause-specific mortality will be calculated.

5.3.4 Disease complications
-Presence of a ventriculoperitoneal shunt (yes/no) B I17, <18 B I17, E I19, <18 E I19
-Any use of anterior pituitary hormone replacement (including thryroid replacement (thyroxine), growth hormone replacement (somatropin), or cortisol replacement (hydrocortisone))(yes/no)

5.4 Statistical Approach

Because of the inherent differences between astrocytomas and ependymomas, survivors with these diagnoses will be analyzed separately. Mediation analysis used in Armstrong *et al.*[8] and Turcotte *et al.*[13] will be applied in this analysis to evaluate the degree to which treatment era effects are mediated by treatment-type changes over the eras as well as change in psychosocial indexes. In addition path analyses will be carried out to understand more complex relationships of direct and indirect effects between treatment factors and outcomes (see more details below).

5.4.1 Primary Aims 4.1.1.1 and 4.2.1.1

For both primary aims, all eligible subjects can be used for the mortality outcomes since National Death Index (NDI) data is available for this larger cohort. However, since treatment data is not available for all non-participants and some participants in the original cohort and a small subset of the expansion cohort, we will plan to impute treatment data using similar methods to those employed by Armstrong *et al.*[8] Descriptive data on demographic and treatment characteristics will be summarized using frequencies, means (SD) and/or medians (Table 1). A graph will be produced that examines treatment type (defined below in appendix) vs treatment era. To accomplish the aims of assessing the all-cause mortality and cause-specific late mortality in astrocytoma and ependymoma survivors 15-year from diagnosis, separate cumulative mortality figures for both astrocytoma and ependymoma survivors will be developed for 1) all-cause mortality, 2) death due to recurrence/progression, and 3) death due to health-related cause. Cumulative mortality will be evaluated by treatment decade (1970s, 1980s, 1990s), by treatment exposures.

SMR will be calculated using age, sex, race/ethnicity and calendar year US mortality rates from the Centers for Disease Control. Rate ratios for all-cause and cause-specific mortality will be calculated and compared across treatment eras and treatment categories, in both univariate (Table 2a) and multivariable Poisson regression analysis (Table 2b) adjusting for sex, age at diagnosis, attained age, and race. A mediation analysis will examine the potential mediating effect of treatment exposures (5.3.3) on the association between treatment era and mortality (Table 3).

5.4.2 Secondary Aims (Astrocytoma)

For 4.1.2.1

Cumulative incidence of subsequent neoplasm (SN) 15 years from diagnosis will be calculated treating death prior to SN as a competing risk. Figures will be provided for cumulative incidence by treatment era and by treatment type (as defined below in appendix). Cumulative incidence will be reported by treatment era and treatment exposure (Tables 4 and 5). Standardized incidence ratios (SIRs) for SMNs will be calculated, using age, sex, race/ethnicity and calendar year U.S. cancer rates from SEER to evaluate the expected number of events. Poisson regression models with expected rates as the offset term will be used to evaluate adjusted comparisons of SMRs by treatment eras and exposure groups. The SMN categories that will be examined may be modified depending on the number of events available once data is examined. Rate ratios comparing the occurrence of SN by treatment era and

exposure to radiation and alkylating agents will be derived adjusting for attained age in a piecewise Poisson model and adjusting for sex, race, NF1 status and either age at diagnosis or years from diagnosis, with each being evaluated in separate models to assess which is most important (Table 6).

For 4.1.2.2
The incidence and severity of chronic health conditions and health status will be determined by using the methodology described previously[14, 15], a comparison will be performed between treatment eras. Cumulative incidence 15 years after diagnosis for three major CHC categories (CTCAE grade 1-5 grade 3-5, and multiple grade 3-5 chronic conditions) will be evaluated (figures to be provided) and Cox proportional hazards models will be used to compare any CTCAE grade 1-5, grade 3-5, and multiple grade 3-5 chronic conditions across treatment eras and reported as hazard ratios with 95% confidence intervals (Table 7a). A model will be fit for which siblings serve as a comparison population. In that model, age will be used as the time scale as siblings do not have a date of diagnosis for reference. Death due to conditions other than those qualifying as a grade 5 fatal chronic condition will be considered as a competing risk event (i.e. death due to recurrence of primary cancer or external causes such as accidents, injuries or suicide). A similar analysis will be performed to correlate the risk of having any grade 1-5, grade 3-5 or multiple grade 3-5 chronic health condition with specific chemotherapeutic treatment data when available (Table 7a). In addition, cumulative incidence of specific grade 1-5 chronic health conditions (Table 7a) will be evaluated across the treatment eras (endocrine, cardiac, pulmonary, neurological, speech). Hazard ratios with 95% confidence intervals for the comparison of each type of outcome across treatment subgroups will be evaluated. A mediation analysis will investigate the mediating and direct effects of treatment variables on the association between treatment era and chronic health conditions (Table 7b).

For 4.1.2.3
Comparison of psychosocial dysfunction in astrocytoma and ependymoma survivors will be carried out across treatment eras and treatment types (Table 8). Psychosocial variables will include individual binary variables contained in Symptom and Attainment Indexes (5.1.5), considered individually. Multivariable comparisons using generalized linear models with either log or logit link will be adjusted for age, gender, NF1 status and ethnicity.

Because proposed associations involving psychosocial variables are complex and because we hypothesize that psychosocial variables are a mediator of the association between treatment era and mortality, we will use a structural equation model approach, specifically a path analysis as shown in the figure below to determine direct and indirect associations between treatment era, treatment exposures, psychosocial variables (Symptom and Attainment Indices) and mortality. All of the variables in our proposed model are observed. The single-headed straight arrows represent a unidirectional "path," where the variable at the point of origin is exerting an influence on the variable that the arrow points toward. Data will be

examined to assure that the necessary conditions for path analysis are present. These conditions include sufficient numbers of observations and values represented, linear and additive relationships, absence of multicollinearity and confounding (or adjustment for relevant confounders), absence of measurement error, inclusion of all nontrival causal variables and ensuring an overidentified model.[16-18] The full path model will be built up, examining each path separately and in a full model with all paths. Iterative reduction will take place, eliminating paths that are not significant, not clinically or statistically interesting (p-value <0.10 or small effect size). Model fitting will be carried out in Mplus. Limitations to this analysis include the possibility of survival bias, since survivors need to be alive at the time of the 2003 survey. Sensitivity analyses stratifying on length of follow-up at the time of the 2003 survey will be undertaken to assess the impact of survival time on the results.

5.4.3 Secondary Aims (Ependymoma)
For 4.2.2.1
Cumulative incidence of subsequent neoplasm (SN) 15 years from diagnosis will be calculated treating death prior to SN as a competing risk. Standardized incidence ratios (SIRs) for SMNs will be calculated, using age, sex, race/ethnicity and calendar year U.S. cancer rates from SEER to evaluate the expected number of events. Figures will be provided for cumulative incidence by treatment era and by treatment type (as defined below in appendix). Cumulative incidence will be reported by treatment era and treatment exposures (Tables 4 and 5). The SMN categories that will be examined may be modified depending on the number of events available once data is examined. Hazard ratios comparing the occurrence of SN by treatment era and exposure to radiation and alkylating agents will be derived using age as the time scale and adjusting for sex, race and either age at diagnosis or years from diagnosis, with each being evaluated in separate models to assess which is most important (Table 6). A path analysis will investigate the effect of treatment variables on the association between treatment era and SN.
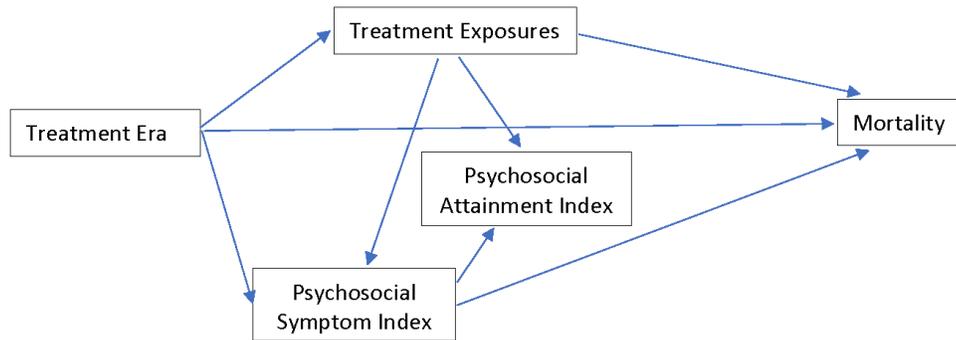
For 4.2.2.2
The incidence and severity of chronic health conditions and health status will be determined by using the methodology described previously[14, 15], a comparison will be performed between treatment eras. Cumulative incidence 15 years after diagnosis for three major CHC categories (CTCAE grade 1-5, grade 3-5, and

multiple grade 3-5 chronic conditions) will be evaluated (figures to be provided) and Cox proportional hazards models will be used to compare any CTCAE grade 1-5, grade 3-5, and multiple grade 3-5 chronic conditions across treatment eras and reported as hazard ratios with 95% confidence intervals (Table 7). A model will be fit for which siblings serve as a comparison population. In that model, age will be used as the time scale as siblings do not have a date of diagnosis for reference. Death due to conditions other than those qualifying as a grade 5 fatal chronic condition will be considered as a competing risk event (i.e. death due to recurrence of primary cancer or external causes such as accidents, injuries or suicide). A similar analysis will be performed to correlate the risk of having any grade 1-5, grade 3-5 or multiple grade 3-5 chronic health condition with specific chemotherapeutic treatment data when available (Table 7). In addition, cumulative incidence of specific grade 1-5 chronic health conditions (Table 7) will be evaluated across the treatment eras (endocrine, cardiac, pulmonary, neurological, vision, hearing, speech). Hazard ratios with 95% confidence intervals for the comparison of each type of outcome across treatment subgroups will be evaluated. A mediation analysis will investigate the effect of treatment variables on the association between treatment era and chronic health conditions.

For 4.2.2.3 (similar to "For 4.2.1.3" above but for ependymoma):
In the subgroup of subjects alive in 2003 (when the last psychosocial outcomes was measured), comparison of psychosocial dysfunction in astrocytoma and ependymoma survivors will be carried out across treatment eras and treatment types (Table 8). Psychosocial variables will include individual variables contained in Symptom and Attainment Indexes (5.1.5), considered individually. Multivariable comparisons will be adjusted for age, gender, NF1 status and ethnicity.

Because proposed associations involving psychosocial variables are complex and because we hypothesize that psychosocial variables are a mediator of the association between treatment era and mortality, we will use a structural equation model approach, specifically a path analysis as shown in the figure below to determine direct and indirect associations between treatment era, treatment exposures, psychosocial variables (Symptom and Attainment Indices) and mortality. All of the variables in our proposed model are observed. The single-headed straight arrows represent a unidirectional "path," where the variable at the point of origin is exerting an influence on the variable that the arrow points toward. Data will be examined to assure that the necessary conditions for path analysis are present. These conditions include sufficient numbers of observations and values represented, linear and additive relationships, absence of multicollinearity and confounding (or adjustment for relevant confounders), absence of measurement error, inclusion of all nontrival causal variables and ensuring an overidentified model.[19] The full path model will be built up, examining each path separately and in a full model with all paths. Iterative reduction will take place, eliminating paths that are not significant, not clinically or statistically interesting (p-value <0.10 or small effect size). Model fitting will be carried out in Mplus. Limitations to this analysis include the possibility of survival bias, since survivors need to be alive at the time of the 2003 survey.

Treatment Exposures

Treatment Era

Mortality

Psychosocial Attainment Index

Psychosocial Symptom Index
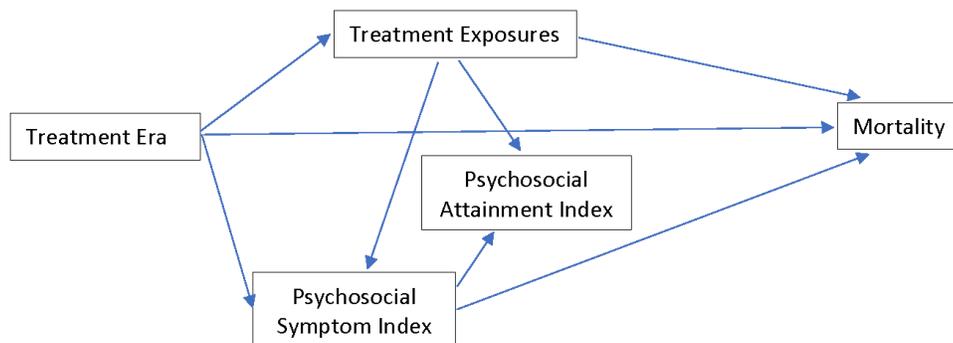
List of figures

Fig 1) a) Distribution of treatment type (defined below in appendix) in each treatment decade, b) Whisker boxplots of psychosocial symptom index vs treatment era, c) Whisker boxplots of psychosocial attainment index vs treatment era.

Fig 2) All-cause mortality (astrocytoma survivors) vs years from diagnosis divided by treatment decade (Fig 2a), treatment exposure (defined below in appendix, Fig 2b), psychosocial indexes (Fig 2c&d).

Fig 3) Cumulative mortality due to recurrence/progression (astrocytoma survivors) vs years from diagnosis divided by treatment decade (Fig 3a), treatment exposure (defined below in appendix, Fig 3b), psychosocial indexes (Fig 3c&d).

Fig 4) Cumulative mortality due to health-related cause (astrocytoma survivors) vs years from diagnosis divided by treatment decade (Fig 4a), treatment exposure (defined below in appendix, Fig 4b), psychosocial indexes (Fig 4c&d).

Fig 5) All-cause mortality (ependymoma survivors) vs years from diagnosis divided by treatment decade (Fig 5a), treatment exposure (defined below in appendix, Fig 5b), psychosocial indexes (Fig 5c&d).

Fig 6) Cumulative mortality due to recurrence/progression (ependymoma survivors) vs years from diagnosis divided by treatment decade (Fig 6a), treatment exposure (defined below in appendix, Fig 6b), psychosocial indexes (Fig 6c&d).

Fig 7) Cumulative mortality due to health-related cause (ependymoma survivors) vs years from diagnosis divided by treatment decade (Fig 7a), treatment exposure (defined below in appendix, Fig 7b), psychosocial indexes (Fig 7c&d).

Fig 8) cumulative incidence of subsequent neoplasm by a) treatment era and by b) treatment type (as defined below in appendix) for both astrocytoma and ependymoma (separately)

Fig 9) cumulative incidence of chronic health conditions [a) CTCAE grade 1-5, b) grade 3-5, and c) multiple grade 3-5 chronic conditions] vs a) treatment decade and b) treatment exposures (defined below in appendix) for both astrocytoma and ependymoma (separately)

Characteristic	Total	1970-1979	1980-1989	1990-1999
All Astrocytoma Survivors				
Age at Diagnosis (N,%)				
<5years				
5-9.9years				
10-14.9years				
>15years				
Age at Most Recent Evaluation (N,%)				
<20 years				
20 – 29.0 years				
30 – 39.9 years				
>40 years				
Race/Ethnicity (N,%)				
Non-Hispanic White				
Non-Hispanic Black				
Hispanic				
Other				
Sex (N,%)				
Male				
Female				
NF Status (N,%)				
Neurofibromatosis type 1 (NF1) negative				
Neurofibromatosis type 1 (NF1) positive				
Chemotherapy Exposure				
Alkylating agents (cumulative cyclophosphamide equivalent dose (mg/m2)) (mean, IQR)				
Cisplatin cumulative dose (mg/m2) (mean, IQR)				
Carboplatin cumulative dose (mg/m2) (mean, IQR)				
Radiation exposure				
Maximum tumor dose (N,%)				
none				
<30Gy				
30–39.9 Gy				
>40 Gy				
Age at radiation in years (median, range)				
Delay in radiation in years (median, range)				
Psychosocial Indexes				
Symptom Index (mean, st dev)				
Unmarried (N, %)				
Unemployed (N,%)				
Uninsured (N,%)				
Education not including college (N,%)				
Income <$20,000/year				
Attainment Index (mean, st dev)				
Impaired emotional distress (N,%)				
Impaired learning/concentration (N,%)				
Pain (N,%)				
Social Isolation (N,%)				

Characteristic	Total	1970-1979	1980-1989	1990-1999
All Ependymoma Survivors				
Age at Diagnosis (N,%)				
<5years				
5-9.9years				
10-14.9years				
≥15years				
Age at Most Recent Evaluation (N,%)	Do we want this to be age at evaluation?			
<20 years				
20 – 29.0 years				
30 – 39.9 years				
≥40 years				
Race/Ethnicity (N,%)				
Non-Hispanic White				
Non-Hispanic Black				
Hispanic				
Other				
Sex (N,%)				
Male				
Female				
Chemotherapy Exposure				
Any chemotherapy exposure (N,%)				
Alkylating agents (cyclophosphamide equivalent dose (mg/m2)) (mean, IQR)				
Radiation exposure				
Maximum tumor dose (N,%)				
none				
<30Gy				
30–39.9 Gy				
≥40 Gy				
Radiation field (N,%)				
whole brain radiation				
focal brain radiation				
Age at radiation in years (median, range)				
Delay in radiation in years (median, range)				
Psychosocial Indexes				
Symptom Index (mean, st dev)				
Unmarried (N, %)				
Unemployed (N,%)				
Uninsured (N,%)				
Education not including college (N,%)				
Income <$20,000/year				
Attainment Index (mean, st dev)				
Impaired emotional distress (N,%)				
Impaired learning/concentration (N,%)				
Pain (N,%)				
Social Isolation (N,%)				

Table 2a: Univariate rate ratios of all-cause late mortality in survivors of childhood glioma and ependymoma

	All cause mortality									
	Total		Total		1970-1979		1980-1989		1990-1999	
	RR	95%CI	SMR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI
All Astrocytoma Survivors										
Year of diagnosis										
1970-1979	reference				N/A		N/A		N/A	
1980-1989					N/A		N/A		N/A	
1990-1999					N/A		N/A		N/A	
Age at Diagnosis (N,%)										
<5years	reference				reference		reference		reference	
5-9.9years										
10-14.9years										
≥15years										
Race/Ethnicity (N,%)										
Non-Hispanic White	reference				reference		reference		reference	
Non-Hispanic Black										
Hispanic										
Other										
Sex (N,%)										
Male	reference				reference		reference		reference	
Female										
NF1 Status (N,%)										
NF1 negative	reference				reference		reference		reference	
NF1 positive										
Chemotherapy Exposure										
Alkylating agents (cyclophosphamide equivalent dose (per mg/m2))										
Cisplatin cumulative dose (per mg/m2)										

Carboplatin cumulative dose (per mg/m2)									
Radiation exposure									
Maximum tumor dose (N,%)									
none	reference				reference		reference		reference
<30Gy									
30–39.9 Gy									
≥40 Gy									
Age at radiation in years (per year)									
Delay in radiation in years (per year)									
Psychosocial Indexes									
Symptom Index									
Lowest tercile	reference				reference		reference		reference
Middle tercile									
Highest tercile									
Attainment Index									
Lowest tercile	reference				reference		reference		reference
Middle tercile									
Highest tercile									
Disease complications									
Presence of a VPS									
Use of ant. pituitary hormone replacement									
All Ependymoma Survivors									
Year of diagnosis									
1970-1979	reference				N/A		N/A		N/A
1980-1989					N/A		N/A		N/A
1990-1999					N/A		N/A		N/A
Age at Diagnosis (N,%)									
<5years	reference				reference		reference		reference
5-9.9years									

10-14.9years										
≥15years										
Race/Ethnicity (N,%)										
Non-Hispanic White	reference				reference		reference		reference	
Non-Hispanic Black										
Hispanic										
Other										
Sex (N,%)										
Male	reference				reference		reference		reference	
Female										
NF Status (N,%)										
Neurofibromatosis type 1 (NF1) negative	reference				reference		reference		reference	
Neurofibromatosis type 1 (NF1) positive										
Chemotherapy Exposure										
Any chemo exposure										
Alkylating agents (cyclophosphamide equivalent dose (per mg/m2))										
Radiation exposure										
Maximum tumor dose (N,%)										
none	reference				reference		reference		reference	
<30Gy										
30–39.9 Gy										
≥40 Gy										
Treatment type										
Focal brain radiation	reference				reference		reference		reference	
Whole brain radiation										
Age at radiation in years (per year)										
Delay in radiation in years (per year)										

Psychosocial Indexes								
Symptom Index								
Lowest tercile	reference			reference		reference		reference
Middle tercile								
Highest tercile								
Attainment Index								
Lowest tercile	reference			reference		reference		reference
Middle tercile								
Highest tercile								
Disease complications								
Presence of a VPS								
Use of ant. pituitary hormone replacement								

Table 2b: Multivariable rate ratios of all-cause and cause-specific late mortality in survivors of childhood glioma and ependymoma, adjusted for sex, age at diagnosis, attained age and race.

	All cause		Recurrence/ Progression		Health-related Cause		Subsequent Neoplasm		Cardiac Cause		Pulmonary Cause		Other Health-related Cause	
	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI
All Astrocytoma Survivors														
Year of diagnosis														
1970-1979	reference													
1980-1989														
1990-1999														
Treatment type														
No radiation	reference													
Delayed radiation (>2years)														
Immediate radiation (<2years)														
Psychosocial Indexes														
Symptom Index														
Lowest tercile	reference													
Middle tercile														
Highest tercile														
Attainment Index														
Lowest tercile	reference													
Middle tercile														
Highest tercile														
All Ependymoma Survivors														
Year of diagnosis														
1970-1979	reference													
1980-1989														
1990-1999														
Treatment type														

Focal brain radiation	reference															
Whole brain radiation																
Psychosocial Indexes																
Symptom Index																
Lowest tercile	reference															
Middle tercile																
Highest tercile																
Attainment Index																
Lowest tercile	reference															
Middle tercile																
Highest tercile																

Table 3: Multivariable relative rate of mortality among five-year survivors of astrocytoma and ependymoma. All analyses adjusted for sex, age at diagnosis, attained age, NF1 status and race

	All Cause		Recurrence/Progression		Health-Related Cause	
	HR	95%CI	HR	95%CI	HR	95%CI
Relative rate of mortality per 5-yr treatment era in <u>Gioma</u> survivors						
unadjusted for therapies or psychosocial indexes*						
adjusted for therapies						
adjusted for abnormal psychosocial symptom index						
adjusted for abnormal psychosocial attainment index						
adjusted for therapies and abnormal psychosocial indexes						
***** **adjusted for sex, age at diagnosis, attained age, race and NF1 status**						
Relative rate of mortality per 5-yr treatment era in <u>Ependymoma</u> survivors						
unadjusted for therapies or psychosocial indexes*						
adjusted for therapies						
adjusted for abnormal symptom symptom index						
adjusted for abnormal psychosocial attainment index						
adjusted for therapies and abnormal psychosocial indexes						
***** **adjusted for sex, age at diagnosis, attained age, and race**						

Table 4: Cumulative incidence of subsequent neoplasms among astrocytoma and ependymoma survivors by treatment era

Astrocytoma		Overall		1970-1979		1980-1989		1990-1999
	N	Cumulative Incidence [95%CI]	N	Cumulative Incidence [95%CI]	N	Cumulative Incidence [95%CI]	N	Cumulative Incidence [95%CI]
Any subsequent neoplasm								
Any subsequent malignant neoplasm								
CNS								
Leukemia								
Lymphoma								
Soft Tissue Sarcoma								
Bone Cancer								
Melanoma								
non-melanoma skin cancer								
non-malignant meningioma								
Other								
Ependymoma		Overall		1970-1979		1980-1989		1990-1999
	N	Cumulative Incidence [95%CI]	N	Cumulative Incidence [95%CI]	N	Cumulative Incidence [95%CI]	N	Cumulative Incidence [95%CI]
Any subsequent neoplasm								
Any subsequent malignant neoplasm								
CNS								
Leukemia								
Lymphoma								
Soft Tissue Sarcoma								
Bone Cancer								
Melanoma								
non-melanoma skin cancer								
non-malignant meningioma								
Other								

Table 5: Cumulative incidence of subsequent neoplasms among astrocytoma and ependymoma survivors by treatment

Astrocytoma	Overall		No radiation		Delayed Radiation		Immediate Radiation	
	N	Cumulative Incidence [95%CI]	N	Cumulative Incidence [95%CI]	N	Cumulative Incidence [95%CI]	N	Cumulative Incidence [95%CI]
Any subsequent neoplasm								
Any subsequent malignant neoplasm								
CNS								
Leukemia								
Lymphoma								
Soft Tissue Sarcoma								
Bone Cancer								
Melanoma								
non-melanoma skin cancer								
non-malignant meningioma								
Other								

Ependymoma	Overall		Whole Brain Radiation		Focal Brain Radiation			
	N	Cumulative Incidence [95%CI]	N	Cumulative Incidence [95%CI]	N	Cumulative Incidence [95%CI]		
Any subsequent neoplasm								
Any subsequent malignant neoplasm								
CNS								
Leukemia								
Lymphoma								
Soft Tissue Sarcoma								
Bone Cancer								
Melanoma								
non-melanoma skin cancer								
non-malignant meningioma								
Other								

Table 6: Multivariable Hazard ratios of subsequent neoplasm in astrocytoma and ependymoma survivors, adjusted for sex, age at diagnosis, attained age, NF1 status and race.

Astrocytoma	Total	Total	Any subsequent neoplasm	Any subsequent malignant neoplasm

	N	SMR [95% CI]	HR [95%CI]	HR [95%CI]
Treatment era				
1970-1979			reference	reference
1980-1989				
1990-1999				
Maximum tumor dose (N,%)				
none			reference	reference
<30Gy				
30–39.9 Gy				
>40 Gy				
Delay in radiation				
0-2 years			reference	reference
2-5 years				
>5 years				
Exposure to alkylating agents (CED)				
lower tercile			reference	reference
middle tercile				
upper tercile				
Ependymoma	**Total**	**Total**	**Any subsequent neoplasm**	**Any subsequent malignant neoplasm**
	N	SMR [95% CI]	HR [95%CI]	HR [95%CI]
Treatment era				
1970-1979			reference	reference
1980-1989				
1990-1999				
Maximum tumor dose (N,%)				
none			reference	reference
<30Gy				
30–39.9 Gy				
>40 Gy				
Radiation field				
focal radiation			reference	reference
whole brain radiation				
Exposure to alkylating agents (CED)				

lower tercile			reference	reference
middle tercile				
upper tercile				

Table 7a: Multivariable hazard ratios of chronic health conditions in astrocytoma or ependymoma survivors by treatment era and treatment type

Astrocytoma	Any grade 1-5	Any grade 3-5	>1 Grade 3-5	Any Endocrine CHC	Any Cardiac CHC	Any Pulm CHC	Any Neuro CHC	Any Vision CHC	Any Hearing CHC	Any Speech CHC
	HR [95%CI]	HR [95%CI]	HR [95%CI]	HR [95%CI]	HR [95%CI]	HR [95%CI]	HR [95%CI]	HR [95%CI]	HR [95%CI]	HR [95%CI]
Treatment era										
1970-1979	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
1980-1989										
1990-1999										
Maximum tumor dose (N,%)										
none	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
<30Gy										
30–39.9 Gy										
>40 Gy										
Delay in radiation										
0-2 years	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
2-5 years										
>5 years										
Exposure to alkylating agents (CED)										
lower tercile	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
middle tercile										
upper tercile										
Psychosocial Score*										
Symptom Index										
Lowest tercile	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
Middle tercile										
Highest tercile										
Attainment Index*										
Lowest tercile	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference

| | Middle tercile | | | | | | | | | |
	Highest tercile									
Ependymoma	Any grade 1-5	Any grade 3-5	>1 Grade 3-5	Any Endocrine CHC	Any Cardiac CHC	Any Pulmonary CHC	Any Neurological CHC	Any Vision CHC	Any Hearing CHC	Any Speech CHC
	HR [95%CI]	HR [95%CI]	HR [95%CI]	HR [95%CI]	HR [95%CI]	HR [95%CI]	HR [95%CI]	HR [95%CI]	HR [95%CI]	HR [95%CI]
Treatment era										
1970-1979	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
1980-1989										
1990-1999										
Maximum tumor dose (N,%)										
none	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
<30Gy										
30–39.9 Gy										
>40 Gy										
Field of radiation										
focal radiation	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
whole brain radiation										
Exposure to alkylating agents (CED)										
lower tercile	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
middle tercile										
upper tercile										
Psychosocial Score*										
Symptom Index										
Lowest tercile	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference
Middle tercile										
Highest tercile										
Attainment Index*										
Lowest tercile	reference	reference	reference	reference	reference	reference	reference	reference	reference	reference

Middle tercile										
Highest tercile										

*Note: Psychosocial indexes compared only to chronic health conditions that occur after the baseline survey; all other analyses include all chronic health conditions

Table 7b: Pathway analysis for chronic health conditions. All analyses adjusted for sex, age at diagnosis, attained age, NF1 status and race.

Astrocytoma	HR [95%CI]
HR of CHC per 10-yr treatment era	
unadjusted for therapies	
adjusted for therapies	
Ependymoma	
HR of CHC per 10-yr treatment era	
unadjusted for therapies	
adjusted for therapies	

Table 8: Multivariable Relative Risk of Heath Status Outcomes across treatment groups, adjusted for age, sex, race and NF1 status.

Astrocytoma	Attainment				Symptom			
	Unmarried	Unemployed	Uninsured	Education <College	Impaired GDI	Impaired learning/ conc	Pain	Social dysfunction
	RR [95%CI]	RR [95%CI]	RR [95%CI]	RR [95%CI]	RR [95%CI]	RR [95%CI]	RR [95%CI]	RR [95%CI]
Treatment era								
1970-1979	reference	reference	reference	reference	reference	reference	reference	reference
1980-1989								
1990-1999								
Maximum tumor dose (N,%)								
none	reference	reference	reference	reference	reference	reference	reference	reference
<30Gy								
30–39.9 Gy								
>40 Gy								
Delay in radiation								
0-2 years	reference	reference	reference	reference	reference	reference	reference	reference
2-5 years								
>5 years								
Exposure to alkylating agents (CED)								
lower tercile	reference	reference	reference	reference	reference	reference	reference	reference
middle tercile								
upper tercile								
	Attainment				Symptom			
Ependymoma	Married	Employed	Insured	Education ≥ College	Impaired GDI	Impaired learning/ conc	Pain	Social dysfunction
	RR [95%CI]	RR [95%CI]	RR [95%CI]	RR [95%CI]	RR [95%CI]	RR [95%CI]	RR [95%CI]	RR [95%CI]
Treatment era								

1970-1979	reference	reference	reference	reference	reference	reference	reference	reference
1980-1989								
1990-1999								
Maximum tumor dose (N,%)								
none	reference	reference	reference	reference	reference	reference	reference	reference
<30Gy								
30–39.9 Gy								
≥40 Gy								
Radiation field								
focal radiation	reference	reference	reference	reference	reference	reference	reference	reference
whole brain radiation								
Exposure to alkylating agents (CED)								
lower tercile	reference	reference	reference	reference	reference	reference	reference	reference
middle tercile								
upper tercile								

Appendix:

For graphical purposes, the following treatment categories will be explored:

-Astrocytoma: two definitions will be examined to determine which better predicts differences in outcomes. These are:

a) no radiation exposure, b) immediate radiation exposure (<2 yrs from diagnosis), c) delayed radiation exposure (>2 yrs from diagnosis), and

a) no radiation exposure, b) radiation exposure in children <6 yrs, c) radiation exposure in children >6 yrs

-Ependymoma: definition of treatment category will be:

a) focal radiation, b) whole brain radiation (defined in 5.3.1.2.2)

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