Study Title: Pooled International Study of Radiation-related Tumors of the Brain and
                   Nervous System

Working Group: Second malignancies

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BACKGROUND AND RATIONALE

While ionizing radiation is a well-established cause of brain and other nervous system tumors, many aspects of these radiation effects remain unresolved due to there being insufficient data in individual studies. Exposure during childhood appears to be more effective in tumor induction than adult exposure, but the data concerning adult exposures are sparse. Little is known about other factors that modify radiation-related risk. The association between radiation exposure and risk appears to be stronger for benign tumors, (meningioma and schwannoma), than for malignant tumors (glioma). Pooled analyses, as well as new data, are needed to better characterize the dose-response for central nervous system (CNS) tumors of various histological types and to evaluate effect modification.

The purpose of this project is to improve our understanding of radiation-related risk for tumors of the brain and CNS by conducting a pooled analysis of epidemiologic studies that have a reasonable number of exposed study subjects and individual estimates of radiation dose. By

including individuals exposed at different ages, for different reasons and at different dose rates, we hope to increase power to quantify the overall dose-response relationship for specific histological types of tumors (glioma, meningioma and acoustic neuroma) and address effects of possible modifying factors. The latter include the influence of age at exposure, temporal patterns of radiation-related risk (in terms of attained age and time since exposure), gender and dose fractionation. We plan to analyze the data for neoplasms of the brain and nervous system using a standardized approach for definition of outcomes and predictors across studies so that we can address issues of variation in risk with host and radiation factors that could not be studied adequately using any single data set. Both excess relative risk and excess absolute risk models will be considered. Gliomas, meningiomas and acoustic neuroma will be evaluated separately. Data for other possible effect modifiers, such as chemotherapy, will be considered, as available. Pooling of fragmentary data contained within individual studies holds promise for filling major gaps in the field concerning radiation-related risks of tumors of the brain and CNS of specific histologic types. In particular, results would aid in the assessment of risks related to cranial computerized tomographic (CT) scans, a question of considerable public health importance in light of the growing use of this diagnostic procedure. The importance of conducting pooled radiation studies of brain tumors is highlighted by the fact that, in the most recent review of health effects of ionizing radiation (BEIR VII), a committee impaneled by the National Research Council judged that available data on brain and CNS neoplasms were insufficient to warrant inclusion of radiation risk estimates for these tumors in their overall cancer risk analysis [1].

The information gained from this study will help to quantify the risk of brain/nervous system neoplasms in populations exposed to ionizing radiation over a broad range of radiation doses, from very low to very high doses, and to assess how other factors modify this risk. The findings will contribute to our knowledge of radiation carcinogenesis and, possibly, provide insights into biologic mechanisms of human cancer induction.

SPECIFIC AIMS

The study objectives are to evaluate:

1) the shape of the radiation dose-response curve, particularly at low doses;

2) the effect of age at irradiation on radiation risk estimates;

3) the effect of sex on radiation risk estimates;

4) temporal patterns of radiation-related risks, in terms of age at risk (attained age) and time since exposure;

5) the effect of dose fractionation; and

6) possible joint effects of radiotherapy and chemotherapy (in studies for which data are available).

ANALYSIS FRAMEWORK

Outcome: All aims will be addressed separately for each major type of brain/CNS neoplasm (glioma, meningioma, and acoustic neuroma). ICDO-3 codes are 9380-9480 for glioma, 9530-9539 for meningioma and 9560 for acoustic neuroma.

Study population: Populations exposed to ionizing radiation from medical, military (atomic bomb) or occupational sources for whom individual radiation dose estimates are available. For CCSS, this includes persons who were in the case-control study reported by Neglia et al. [2]. That study included 40 glioma cases, 66 meningioma cases, and 464 controls. No additional CCSS participants will be added beyond those included in that study. Fourteen other eligible study populations have been identified, and principal investigators have tentatively agreed to participate (Appendix 1). In aggregate, the proposed pooling study will include more than 920 cases of brain or CNS neoplasms (including tumors of cranial nerves) diagnosed among more than 275,000 persons exposed to ionizing radiation.

Explanatory variables: Radiation dose to site of second primary CNS tumor, chemotherapy (class of agent and dose, as available), type of first cancer, age at first cancer, gender, race, year of birth, age at CNS tumor diagnosis, year of CNS tumor diagnosis

Statistical analysis: Data analysis will be conducted at NCI. Dr. Dale Preston, formerly Chief of the Statistics Department at the Radiation Effects Research Foundation in Hiroshima, will serve as statistical consultant. He has extensive experience in conducting pooled analyses and previously led an analysis of nervous system tumors among atomic bomb survivors that will contribute to this analysis.

For pooled analyses of cohort and case-control studies, we will use a likelihood function

that combines binomial and Bernoulli probabilities. For rare diseases, a binomial distribution closely approximates a Poisson distribution. For each cell of the person-years cross-tabulation, we will assume a binomial distribution, where the number of cases represented the "successes" from person-time "trials". In this instance, the likelihood is the product of cell-specific binomial and case-control subject-specific Bernoulli probabilities.

We will evaluate the dependence of the relative risk or the absolute risk (for cohort studies) on exposure level, age at risk, age at exposure, time since exposure, gender, and other relevant risk factors.

The initial analyses for either the binomial or Poisson regressions will utilize a standard log-linear model for the RR, i.e., $RR = \exp(\theta x)$, where x is a vector of explanatory variables and θ is the associated vector of parameters. We will further examine the radiation dose-response relationship using both an excess relative risk (ERR) model:

$$\lambda(x,z,d) = \lambda_0(x) \{1 + ERR(d,z)\} \qquad (1)$$

and, for the cohort studies only, an excess absolute risk (EAR) model:

$$\lambda(x,z,d) = \lambda_0(x) + EAR(d,z) \qquad (2)$$

where $ERR(d,z)$ and $EAR(d,z)$ represent the excess relative risk and excess absolute risk, respectively, in terms radiation dose, d, and other factors, z, and where $\lambda_0(x) = \exp(\theta x)$ describes the brain/nervous system neoplasm incidence rate among non-exposed patients in terms of covariates x.

To evaluate the shape of the dose-response (the ERR and the EAR) we will fit general linear-exponential models:

$$ERR(d) = \beta d \exp(\gamma_1 d + \gamma_2 d^2) \qquad (3)$$

Including the simple linear model, $\gamma_1 = \gamma_2 = 0$, linear-exponential (linear) model $\gamma_2 = 0$, and linear-exponential (quadratic) model, $\gamma_1 = 0$. We will also consider the extension where βd will be replaced by $(\beta_1 d + \beta_2 d^2)$.

Using the best fitting dose-response model, we will evaluate multiplicative interaction of the ERR and EAR with sex, attained age, age at exposure, time since exposure, dose-fractionation and some study-specific characteristics (type of first cancer, chemotherapy, etc.).

We will base hypothesis tests on likelihood ratio tests and calculate 95% CIs using a profile likelihood. Statistical analyses will be run in the Epicure program [3], with the AMFIT module used for Poisson regression and the GMBO module used for regression for the case-control

analyses and for the Bernoulli/binomial regression of pooled data.

While the primary objective of this proposal is the pooled analysis, we envision a stepwise approach. First, we will analyze overall results for each study separately to confirm consistency with previously published results. Next, we will combine results for related studies, including studies of: (1) second brain/CNS cancer in childhood cancer survivors; (2) brain/CNS cancers after any childhood radiation exposures; (3) brain/CNS cancer after adult exposures. The final aggregation will be over all sources of exposure and all ages at exposure. At this time, we anticipate that the latter will be the primary focus of a single publication covering all tumor types, with the other analyses providing insights into understanding patterns of heterogeneity in the data and to be included as supplemental material; however, it is possible that this approach would be unwieldy and that the analysis would argue for partitioning results into more than one manuscript. This would be a topic for discussion by the study collaborators, including at the proposed organizational meeting in March 2013.

SPECIFIC TABLES AND FIGURES [a,b]

Table 1. Characteristics of CNS tumor patients for each study and for all pooled data combined.

Table 2. Relative risk of CNS tumor by radiation dose categories for each study and for all data combined.

Table 3. Relative risk of CNS tumor and chemotherapy, by categories of radiation dose.

Table 4. Estimates of modification of linear component of radiation dose-response relationship for all data combined [gender, age at exposure, years since first exposure, attained age, type of first cancer (as applicable), chemotherapy (as applicable)]

Figure 1. Relative risks and 95% confidence intervals for categories of radiation dose and fitted dose-response models for all data combined.

[a] Separately for glioma, meningioma and acoustic neuroma

[b] Some study-specific analyses may be presented in supplemental tables.

REFERENCES

1. Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII, Phase 2 (2006). Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiaiton, Board on Radiation Effects, Research Division on Earth and Life Studies. Washington, D.C.: National Research Council of the National Academies3.

2. Neglia JP, Robison LL, Stovall M, Liu Y, Packer RJ, et al. (2006) New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Natl Cancer Inst 98: 1528-1537.

3. Preston DL, Lubin JH, Pierce DA, McConney ME, editors (1993) Epicure. Seattle, WA: HiroSoft International Corporation.

Appendix 1. Study Populations

Patients treated for cancer

US Childhood Cancer Survivor Study
British Childhood Cancer Survivor Study
Late Effects Study Group cohort of childhood cancer survivors
Nordic countries case-control study of childhood cancer survivors
European childhood cancer patients cohort

Patients treated for benign diseases

Israel tinea capitis study
New York tinea capitis study
Michael Reese Hospital cohort of children irradiated to the head and neck
Hemangioma study of irradiated infants – Göteborg
Hemangioma study of irradiated infants - Stockholm
Hemangioma study of irradiated infants – Institut Gustav Roussy, France

Diagnostic exposure

British cohort study of diagnostic CT exposure

Military exposures

Life Span Study of Atomic Bomb Survivors

Occupational exposures

Mayak cohort of nuclear workers

UK radiation workers (participation decision pending)