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Frequency and Severity of Health Conditions Seen in Pediatric Brain Tumor Survivors: A Pilot Study

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B.A., Rice University, 1999
M.D., Emory University, 2003

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An abstract of
A thesis submitted to the Faculty of the James T. Laney School of Graduate Studies of Emory University
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Abstract

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By Briana Cary Patterson

Background. As an increasing number of pediatric cancer patients are becoming long-term survivors, it becomes important to understand the frequency and severity of the health conditions that may be consequences of cancer therapies. National guidelines direct the surveillance for late effects of cancer therapy. Surveillance is individualized and agent-specific. The purpose of this pilot study is to estimate the frequency and severity of health conditions in a pediatric brain tumor survivor program and compare them to that seen in a non-brain tumor cancer survivor population.
Methods. Pediatric and young adult brain tumor survivors were recruited prospectively. Patients were evaluated with history, physical and testing as per the Children's Oncology Group *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancers*. Data collected included demographic information, cancer treatments, and a list of health conditions. Health conditions were scored for severity (1, mild to 5, death) according to the Common Terminology for Adverse Events (CTCAE v. 4.03). Brain tumor survivors were compared to other pediatric and young adult survivors of non-central nervous system childhood cancers seen in the Cancer Survivor Program. Brain tumor survivors were matched 1:2 to other survivors on gender and age at cancer diagnosis.
Results. 330 health conditions were observed in the brain tumor survivors and 163 health conditions were observed in the other cancer survivors. The mean number of conditions per survivor was higher in brain tumor survivors than other survivors. Brain tumors survivor were more likely to have at least one cardiac, opthamologic/otolaryngological, neurological, or dermatologic/musculoskeletal condition. The median maximum CTCAE severity score per survivor was higher in the brain tumor group. In a multivariate conditional logistic regression model, brain tumor diagnosis was associated with having at least one severe or life-threatening health condition. In a linear regression model, radiation was associated with an increased number of health conditions among brain tumor survivors.
Conclusions. In conclusion, this pilot data demonstrates increased frequency and severity of health conditions in pediatric brain tumor survivors relative to other pediatric cancer survivors. This study serves to inform additional research to understand the associations between brain tumor treatments and adverse health outcomes.

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Tables and Figures

Introduction

Although survival for pediatric cancers has improved(1), cancer therapy, including surgery, chemotherapy, and radiation, often results in chronic health conditions, also known as late effects of cancer therapy(2). The Aflac Cancer Center and Blood Disorders Service of Children's Healthcare of Atlanta has about 350 new cancer diagnoses annually, which includes approximately 90 new brain tumor patients. The Cancer Survivorship Program (CSP) was started in 2001 to screen for late effects in patients who are at least 2 years off therapy. Currently, about 900 non-brain tumor survivors have been seen and evaluated for late effects.

The patients attending the CSP have been previously described(3). However, historically, brain tumor patients have not been routinely seen in the CSP and were not included in this prior analysis. Thus, in conjunction with initiation of a clinical program to target pediatric brain tumor survivors for formal survivorship care, this study seeks to characterize the frequency and severity of health conditions in pediatric brain tumor survivors and to compare them to other pediatric cancer survivors. By recruiting the brain tumor survivors as they attended the survivor clinic, health conditions, as well as demographic variables, can be ascertained and documented prospectively. This pilot study seeks to describe the frequency and types of health conditions and to compare these between brain tumor survivors and other cancer survivors. All conditions are scored for severity according to the Common Terminology Criteria for Adverse Events (CTCAE)(4, 5), and treatment factors associated with occurrence of adverse health outcomes are investigated.

Background

Overall, nearly 80% of pediatric cancer patients can be expected to have long term survival(1). However, 62% of adult survivors of pediatric cancers have been reported to have at least one chronic health condition. Among these survivors, 28% were found to be severe or life threatening(2). Because of the risk of late effects after cancer therapy, the Institute of Medicine recommends that every cancer survivor be knowledgeable about their cancer treatment and risks for late effects and have a Survivor Healthcare Plan(6). This plan includes a summary of cancer treatment, an individualized late effects risk profile and surveillance plan for late effects. Unfortunately, prior research has shown that the majority of pediatric cancer survivors do not receive the appropriate risk-based care(7).

The *Children's Oncology Group Long-Term Follow-Up Guidelines* (COG-LTFUG)(8) were developed to serve as evidenced-based, cancer therapy-specific recommendations for screening for late effects(9). Thus, the COG-LTFUG can be used to individualize Survivor Healthcare Plans for pediatric cancer survivors. The COG-LTFUG are reviewed by multi-disciplinary task forces and updated every 2 years based on review of the published medical literature. The goals for clinical application of these guidelines are early identification of late effects, timely intervention for late effects, promotion of healthy lifestyles, and reduction in healthcare costs. The effectiveness of these guidelines has not been prospectively evaluated(10).

Survival rates for pediatric brain tumor patients are also improving. For example, 5-year progression- free survival rates are reported as high as 80-85% for non-disseminated

medulloblastoma and over 95% for low grade gliomas after gross total resection(11). To achieve these outcomes, brain tumor patients are often exposed to multi-modal cancer therapy, which may include surgery, chemotherapy and radiation therapy(12). Thus, brain tumor patients may be at increased risk for late effects due to the intensity of cancer treatment protocols or due to the tumors themselves. An increased burden of adverse neuro-cognitive and endocrine outcomes has been reported in adult survivors of pediatric brain tumors relative to siblings and survivors of other cancers(13-16). Although, generally, adolescent and young adult cancer survivors have been shown to exhibit resiliency, these health conditions have the potential to negatively impact quality of life, and may be a source of anxiety for survivors(17) and their families. Indeed, parental anxiety about treatment and outcome has been reported to be increased in pediatric brain tumors relative to non-central nervous system (CNS) malignancies(18), and health-related quality of life outcomes have been reported to be poorer in pediatric brain tumor survivors compared to other survivors of pediatric cancers(19).

In our center, prior research on pediatric-aged cancer survivors, excluding brain tumor survivors, has documented that 88% have at least one health condition, and 36% have a severe/life-threatening condition(3). This is a higher rate of health conditions than what has been observed in adults with similar cancer histories(2). One possible reason for the observation of a higher rate of health conditions in the younger pediatric patients is that the study of adult aged survivors ascertained health conditions and their severity by self-report, and our pediatric study ascertained health conditions and their severity from the problem lists generated during formal clinical evaluations. Historically, survivors of

pediatric brain tumors were not followed in this center's survivor clinic. Thus, the health conditions of pediatric brain tumor survivors were not described in our prior study.

Methods

The Brain Tumor Survivor Clinic (BTSC) and Cancer Survivor Program (CSP) are clinical services in the Aflac Cancer Center and Blood Disorders Service of Children's Healthcare of Atlanta. The programs offer long term follow-up to pediatric and young adult-aged survivors of pediatric cancers. All patients attending the BTSC and Cancer Survivor Program are referred by their treating oncologists and experience a comprehensive evaluation. Prior to the visit, the medical records related to their cancer treatments are reviewed and summarized. The modalities of treatments (chemotherapy, radiation, etc), the specific agents, and doses are summarized. The COG-LTFUG are applied and patients are assessed in an individualized fashion based on the recommendations of the Survivor Healthcare Plan. A problem list is generated for each patient based on the records provided by the referring oncologist, history, physical exam, and the results of testing performed at the visit. The treatment history, recommended late effects surveillance, the results of testing and the problem list are entered into a clinical database for all patients. The evaluation process in the CSP and the BTSC are the same.

Hypotheses

The hypotheses are stated below in null form:

Hypothesis 1. The number of health conditions per subject in the pediatric brain tumor cancer survivor group will be statistically equal to the number of health conditions per subject in the group of other pediatric cancer survivors.

Hypothesis 2a. The median severity score for pediatric brain tumor survivors will be statistically equal to that of other pediatric cancer survivors.

Hypothesis 2b. The odds ratio of a grade 3 or 4 event comparing pediatric brain tumor survivors versus other pediatric cancer survivors, controlling for treatment and demographic variables, will be equal to 1.

Hypothesis 3. Within the pediatric brain tumor survivors, subjects exposed to chemotherapy or radiation therapy will have numbers of health conditions equal to subjects not exposed to these therapies, controlling for age of diagnosis, time since tumor diagnosis.

Hypothesis 4a. The number of endocrine health conditions per subject in the pediatric brain tumor cancer survivor cohort will be statistically equal to the number of chronic health conditions per subject in the other pediatric cancer survivor cohort.

Hypothesis 4b. Within the pediatric brain tumor survivors, subjects exposed to chemotherapy or radiation therapy will have numbers of endocrine conditions equal to those not exposed to those treatments, controlling for age, time since tumor diagnosis

Study Design

This is a cross-sectional observational study, analyzed as a case-control study.

Subjects

Brain tumor survivors were recruited prospectively from the BTSC. Patients attending the BTSC were referred by their neuro-oncologist, and all were diagnosed with a brain tumor prior to age 18 years. Inclusion criteria were prior diagnosis with a tumor of the central

nervous system and no cancer-directed therapy for a minimum of 2 years prior to the BTSC visit. Exclusion criteria included an initial cancer outside the central nervous system. Hence, patients with metastatic disease in the central nervous system or with a central nervous system tumor as a second malignancy were excluded.

Brain tumor survivors were recruited prospectively and all participating brain tumor survivors over age 17 years provided informed consent. For subjects under age 18 years, consent was obtained from the parent or guardian. Verbal or written assent as appropriate was obtained from children at least 6 years old. For this pilot study, participation was offered to 29 subjects, and 28 consented to participate. This study was approved by the Institutional Review Boards of Emory University and Children's Healthcare of Atlanta.

Brain tumor survivors were compared to survivors of other types of cancers. The comparison group consisted of 519 survivors of other cancers that had been previously evaluated in the Cancer Survivor Program between 2001 and 2005. Data on the other survivors were collected retrospectively in an IRB approved study with waived consent. From the 519 subjects available for comparison, other cancer survivors were matched to brain tumor survivors 2 to 1 on gender and age at diagnosis. The 519 other brain tumor survivors were grouped by gender and age at diagnosis in 2 year intervals. Within each group, subjects were randomly selected as needed to match the brain tumor survivors. This yielded 56 other survivors for the analysis.

Variables

Data were collected from the clinical database. Predictor variables included age at diagnosis (continuous; years), gender (dichotomous), race (categorical; white, black, Hispanic, other), age at cancer survivor clinic visit (continuous; years), cancer diagnosis, chemotherapy (dichotomous; Yes/No), radiation therapy (dichotomous; Yes/No), history of relapse (dichotomous; Yes/No).

For each subject, a list of health conditions was generated. All health conditions were categorized by organ system affected (endocrine, cardiac, neurological, etc.). All health conditions were scored for severity according to the CTCAE (1 to 4; 1 is mild, 4 is life-threatening). The CTCAE designates for a score of 5 to be assigned for fatal events; however, due to the design of recruiting living subjects from the clinic, there were no grade 5 events. Outcome variables included the number of health conditions per subject (ordinal, pseudo-continuous), presence of at least one grade 3 or 4 condition (dichotomous; Yes/No), the number of endocrine health conditions per subject (ordinal, pseudo-continuous), the maximum severity score per subject (ordinal; 1 to 4). Because the severity scores are not interval, summation of all severity scores per subject was not appropriate. For example, the aggregate health impact of five mild conditions (Grade 1) should be assumed to be equivalent in severity to the health impact of a single fatal condition (Grade 5). Thus, the maximum severity score per subject was chosen for analysis as a summary measure of the severity of the health conditions of each subject. For subjects with no health conditions, a maximum severity score of 0 was assigned. For

each subject, it was also determined if the subject had at least one health condition in each of 12 organ system categories (12 dichotomous outcomes; Yes/No).

Statistical analysis

All analysis was conducted with SAS v 9.2 (Cary, NC). Two sample t-tests were used to compare means for continuous and pseudo-continuous variables. The central limit theorem was applied to satisfy the assumption of normality. Maximum severity score per subject was an ordinal variable, but not interval, thus the Wilcoxon rank sum test was used to compare medians. Chi-square tests and Fisher Exact tests (if cell counts <5) were used to compare proportions for categorical variables. For all analysis, the significance level was $\alpha=0.05$. Where appropriate, a Bonferroni correction for multiple hypothesis testing was applied.

Because many subjects had more than one condition, individual health conditions were not independent. To depict the distribution of all health conditions by affected organ system and the distribution of severity scores of all health conditions, histograms were used. In these descriptions, no statistical comparison could be made between brain tumor survivors and other survivors due to lack of independence.

To investigate the association between brain tumor diagnosis compared to other cancer diagnosis with the outcome of having a severe or life threatening event (maximum severity score ≥ 3) controlling for treatment and demographic variables, conditional logistic regression was used. A conditional model was chosen because the subjects were

matched on age at cancer diagnosis and gender. Univariate conditional logistic regression was performed for the variables of interest, and a final multivariate model was selected based on the significance of variables in the univariate models and investigator preference.

To investigate the treatment and demographic factors influencing the number of health conditions per subject among brain tumor survivors, linear regression was used. Correlations were run between each predictor and the number of health conditions per subject. Simple linear regression was used to assess each variable individually as well, and the final multiple linear regression model was selected using an all possible regressions strategy with final model selection at the discretion of the investigator, utilizing the R-squared and Mallow's Cp to avoid over-fitting.

Power and Sample size

Because this is a pilot study with a relatively small sample size, a post hoc power analysis was conducted. For the t-test comparing the mean number of health conditions per subject between brain tumor survivors (n=28) and other survivors (n=56), with significance level, α, set at 0.05, the power was calculated to approach 1.0. For the comparisons of the proportions of subjects affected with health conditions in each organ system, post hoc power was calculated for each comparison. The anticipated sample sizes needed to achieve power of 0.8 based on the proportions observed in this pilot study were also calculated (Table 1). For the simple linear regressions estimating the effect of treatment and demographic variables on the outcome variable, number of health

conditions, a post hoc power analysis was conducted. The anticipated sample sizes needed to achieve power of 0.8 based on the observations in this pilot study were also calculated, assuming λ, the desired slope of the line to be detected, was set a 1 for all dichotomous variables and set to 0.25 for the continuous time variables (Table 2).

Results

Demographic and treatment data for 28 pediatric brain tumor survivors and 56 other pediatric cancer survivors are shown in Table 3. The cancer diagnoses of the subjects are shown in Table 4. The most common brain tumor diagnosis was medulloblastoma, and the most common other cancer diagnosis was leukemia.

Overall, a total of 330 health conditions were observed the pediatric brain tumor survivors and 163 health conditions were observed in the other pediatric cancer survivors. There were significantly more health conditions per subject in the brain tumor survivors compared to the other survivors ($p<0.001$, t-test). For brain tumor survivors, the mean number of conditions per subject was 11.7 (minimum 2, maximum 20; 95% confidence interval of the mean 9.7, 13.8). For other cancer survivors, the mean number of conditions per subject was 2.9 (minimum 0, maximum 10; 95% confidence interval of the mean 2.3, 3.5). The total numbers of health conditions observed categorized by affected system are shown in Figure 1. There were significantly higher proportions of brain tumor survivors affected with cardiac, opthamologic/otolaryngological, neurological, and dermatologic/musculoskeletal conditions (Table 5).

With respect to the severity of the health conditions observed, CTCAE severity scores ranged from 1-4. No grade 5 (fatal) conditions were observed due to the study design which included only living subjects. The distribution of CTCAE severity scores for all the health conditions observed in pediatric brain tumor and other survivors is shown in

Figure 2. The distribution of the maximum CTCAE severity score per survivor is shown in Figure 3. There were no brain tumor survivors without any health conditions and 7 other cancer survivors with no health conditions (maximum CTCAE severity score assigned 0). The median of the maximum severity scores in brain tumor survivors was significantly higher (median 3; minimum 1, maximum 4) than the median of the maximum severity scores in other survivors (median 2; minimum 0, maximum 4) ($p = 0.002$, Exact Wilcoxon rank sum test, 2-sided).

The conditional logistic regression model for the outcome of a subject having at least one grade 3 (severe) or grade 4 (life-threatening) health condition is shown in Table 6. Prior brain tumor diagnosis, as opposed to prior other cancer diagnosis, was associated with higher risk of having a grade 3 or 4 outcome, controlling for history of radiation, chemotherapy, and time between tumor diagnosis and survivor visit. The model also controls for age at cancer diagnosis and gender, which were the matched variables.

A model investigating the demographic and treatment variables associated with the numbers of health conditions among brain tumor subjects is shown in Table 7. The final model selected includes chemotherapy and radiation therapy. Radiation therapy was significant in the model ($p=0.001$). Prior treatment with radiation was associated with an increased in the number of health conditions by 6.95.

With respect to the frequency of endocrine conditions observed, there were significantly more endocrine health conditions per subject in the brain tumor survivors compared to

the other survivors ($p<0.001$, t-test). For brain tumor survivors, the mean number of endocrine conditions per subject was 2.9 (minimum 0, maximum 6; 95% confidence interval of the mean 2.2, 3.6). For other cancer survivors, the mean number of endocrine conditions per subject was 0.8 (minimum 0, maximum 3; 95% confidence interval of the mean 0.6, 1.1).

A model investigating the demographic and treatment variables associated with the numbers of endocrine health conditions among brain tumor subjects is shown in Table 8. The final model selected includes radiation therapy and time between diagnosis and survivor visit. Both variables were significant in the model ($p=0.015$ and 0.028, respectively). Prior treatment with radiation was associated with an increased in the number of endocrine health conditions by 1.81. Each additional year of time elapsed between the brain tumor diagnosis and survivor clinic evaluation was associated with an increased in the number of endocrine health conditions by 0.2.

Discussion

This pilot study demonstrated a higher frequency of health conditions and endocrine conditions compared to other survivors. The severity was greater in brain tumor survivors compared to other survivors. Among brain tumor survivors, radiation was associated with an increase in the number of health conditions and endocrine conditions. Time since cancer treatment was associated with an increase in the number of endocrine conditions.

The strengths of the study include that data was collected prospectively from the brain tumor patients. The estimates of the outcome variables and their distributions could be used to make post hoc estimates of power in this pilot study. Our center has a large number of brain tumor patients available for study, and recruitment is continuing. Power calculations from this pilot study will inform our ongoing investigation.

Sometimes brain tumor survivors are not targeted for survivor research, perhaps because their history and outcomes are more complex, or perhaps because the risk of late recurrence is higher. Our study focuses on the outcomes of pediatric brain tumor survivors, and includes a diverse group of brain tumor patients. This is a strength insofar as a wide range of treatments and outcomes is represented in our study sample. However, variability in the diagnoses, the types of prior chemotherapy exposures, and the radiation exposures (modalities, fields treated, and doses) could also be considered a weakness. In this study, the goal was to broadly describe the outcomes for the group of brain tumor

survivors; however, the heterogeneity of the study group limits the general application of the conclusions when considering individual patients.

Referral and selection bias are also a concern in this study. Only those who were referred and elected to come to clinic could be recruited. Our recruitment rate among eligible brain tumor survivors attending clinic was high (97%). However, there is the possibility of bias at several levels prior to clinic attendance. This includes bias with respect to the selection of patients by their neuro-oncologists to be referred and with respect to which referred patients actually scheduled and arrived to a survivor clinic appointment. Indeed, prior research in the Childhood Cancer Survivor Study has suggested that survivors seeking care have and increased number of health conditions compared to those without a recent visit to a healthcare provider(20).

Amongst the brain tumor study population, there may be some unique barriers to clinic attendance. Brain tumor patients are typically still having ongoing follow-up with their neuro-oncologists on an annual basis; where as, the other pediatric cancer survivors have most commonly been discharged from the oncology clinic. Brain tumor patients may be reluctant to make an extra visit to the cancer center if they view the survivor care as redundant to their neuro-oncology visits. On the other hand, a survivor who has been discharged from the oncology clinic may be reluctant to return to the cancer center, even for a survivor appointment.

In the comparison group of other pediatric cancer survivors, prior work in our center demonstrated that Caucasians and sarcoma survivors were over-represented relative to the expected numbers of survivors based on new cancer diagnoses in our center (3). In this data among brain tumor survivors, the proportion of Caucasians was similar to that observed in the other survivor group, suggesting that this bias may be present in the current study as well. This supports the appropriateness of the comparison group, but limits the general application of the conclusions to other racial groups.

Because brain tumor survivors and other cancer survivors were matched on age at cancer diagnosis and gender, those variables are controlled for in the analysis, but the magnitude of their effect on outcome variables, if any, could not be determined. The matched analysis was chosen to control for confounding and improve power given the small sample size of the pilot study. However, age at cancer diagnosis is a potentially interesting variable because the vulnerability of the patients to late effects of treatment may depend on their age at the time of the treatment. In future studies, it would be desirable to include this variable in the analysis.

Regarding gender, with the exception of some of the endocrine outcomes, such as precocious puberty and fertility outcomes, it seems biologically implausible that gender would be causally related to the health condition outcomes in young subjects. However, because some outcomes can only be experienced by a single gender (i.e. dysfunction uterine bleeding or erectile dysfunction), these outcomes are by definition are associated with gender. Gender likely does not function as a classic confounder, though, because

one would not expect that gender is associated with the predictor variables (brain tumor diagnosis versus other cancer diagnosis, radiation treatment, etc.). However, because gender was a matched variable, it is not possible to investigate the effects of gender or to assess for interaction with gender.

Additionally, data for this study is cross-sectional, and the follow-up period after the cancer diagnosis was variable. Thus, the data cannot be used to estimate incidence of health conditions. A variable representing the time between the cancer diagnosis and the survivor clinic visit was included to attempt to control for the variability in follow-up time. Indeed, this time was greater in the brain tumor group than in the other cancer survivors. However, time between the cancer diagnosis and the survivor clinic visit cannot be assumed to be equivalent to the time between the cancer diagnosis and the onset of the health conditions. Thus, it is not the true "time at risk," and no survival analysis can be performed due to this.

Finally, while it is plausible that the cancer treatments resulted in the observed health conditions, no causal inferences can be made due to the study design. Prior research supports the association between chemotherapy, radiation therapy and surgery and the development of health conditions, including the types of health conditions that were observed in this study. It seems unlikely that the health conditions observed caused the cancers (i.e., short stature would not be expected to cause a brain tumor). However, our study did not differentiate conditions that originated prior to the cancer diagnosis from those that had onset after the cancer diagnosis. Further, some conditions arising after the

cancer diagnosis may be causally unrelated to it. Thus, this study does not establish causation.

This pilot study also demonstrated differences in the frequency of health conditions not specifically addressed here. With additional sample size, further studies will investigate the relationship between treatment variables and other health outcomes (i.e. neurological, hearing, vision). The pilot study reported here included relatively few subjects treated with surgery only; thus this treatment variable was not included for this analysis. However, it is plausible that some health conditions are a direct result of neurosurgical intervention or of the tumor itself, and not due to chemotherapy or radiation. Recruitment of a group of brain tumor subjects treated only with surgery for comparison to brain tumor subjects exposed to multimodal therapy would improve understanding of the role of surgery.

In conclusion, this pilot data demonstrates increased frequency and severity of health conditions in a group of pediatric brain tumor survivors relative to other pediatric cancer survivors. The information developed here about the variability of treatments and outcome variables should inform additional research to understand the associations between brain tumor treatments and adverse health outcomes. Further research is needed to determine the effectiveness of current national screening guidelines for the detection of late effects in pediatric brain tumor survivors and to develop interventions to minimize the incidence and impact of late effects in this population.

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TABLES

Table 1. Post hoc power and sample size calculations for comparisons of the proportions of survivors affected by at least one health condition in each category with Chi-squared or Fisher exact tests.

System Affected	Post hoc power	Sample size needed to achieve power=0.80	
		Brain tumor survivors	Other survivors
Cardiac	0.665	36	72
Dental	0.124	158	316
Endocrine	0.363	49	98
Gastrointestinal	0.390	60	120
HEENT	*	9	18
Hematological	**	**	**
Neurological	*	11	22
Neuropsychological	0.436	48	96
Pulmonary	0.267	79	158
Renal/genitourinary	0.107	153	306
Skin/musculoskeletal	0.740	30	60
Second malignancies	**	**	**

Both power and sample size calculations assume that the individual significance level for each comparison is 0.004. This utilizes the Bonferroni correction for multiple hypothesis testing.

*Achieved significance in this pilot study.

**Because no events were observed in one of the groups, no power or sample size calculations were performed.

Table 2. Post hoc power and sample size calculations for simple linear regression investigating the relationship between treatment and demographic variables and the dependent variable, the number of health conditions observed among brain tumor patients.

Independent Variable	**Post hoc power**	**Sample size needed to achieve power=0.80**
Chemotherapy	0.070	1069
Radiation	0.078	762
Age at tumor diagnosis, yr	0.211	147
Time between tumor diagnosis and survivor visit, yr	0.147	235
Relapse	0.283	951
Gender	0.073	952

For the power calculations above, λ, the slope of the line to be detected, is set a 1 for all dichotomous variables (chemotherapy, radiation, relapse and gender). For the continuous variables Age at tumor diagnosis (yr) and Time between tumor diagnosis and survivor visit (yr), λ, the slope of the line to be detected, is set a 0.25. The type I error rate is set at 0.05. For each of these calculations the standard deviation of the regression errors was estimated from the standard deviation of the independent variable, the correlation coefficient between the independent and dependent variables, and the observed slope of the regression line from the data in this pilot study.

Table 3. Demographic and treatment data for pediatric brain tumor survivors and other pediatric cancer survivors, matched 1:2 on gender and age at diagnosis.

	Brain tumor survivors	Other survivors	p-value
Total Subjects	28	56	
Gender, n			
Female	15	30	
Male	13	26	
Race, n (%)			0.509[a]
White	22 (79%)	41 (73%)	
Black	4 (14%)	7 (13%)	
Hispanic	0	5 (9%)	
Other	2 (7%)	3 (5%)	
Relapse, n (%)	9 (32.1%)	9 (16.1%)	0.091[b]
Treatment			
Chemotherapy, n (%)	21 (75%)	56 (100%)	<0.001[a]
Radiation, n (%)	21 (75%)	18 (32.1%)	<0.001[b]
Mean age at diagnosis, years (95% CI)	7.1 (5.2, 9.1)	6.7 (5.3, 8.1)	
Mean time, diagnosis to survivor visit (95% CI)	9.9 (8.5, 11.3)	6.5 (5.6, 7.5)	<0.001[c]

[a]Fisher exact test
[b]Chi-squared test
[c]Two sample T-test

Table 4. Diagnoses in pediatric brain tumor survivors and other matched pediatric cancer survivors (numbers of subjects).

Diagnosis	**Brain tumor survivors**	**Other survivors**
Medulloblastoma	10	
Glioma	5	
Astrocytoma	3	
Craniopharyngioma	3	
Optic pathway glioma	2	
Central nervous system germ cell tumor	2	
Other brain tumor	3	
Leukemia		27
Renal tumors		9
Sarcoma		6
Neuroblastoma		6
Hodgkins		4
Non-Hodgkin lymphoma		3
Non-central nervous system germ cell tumor		1

Table 5. Number and proportion of subjects affected with at least one health condition by system affected, number of subjects (%).

System Affected	Brain tumor	Other survivors	P-value
Cardiac	11 (39.3%)	5 (8.9%)	<0.001[a*]
Dental	6 (21.4%)	5 (8.9%)	0.109[a]
Endocrine	25 (89.3%)	33 (58.9%)	0.005[b]
Gastrointestinal	11 (39.3%)	8 (14.3%)	0.010[a]
HEENT	23 (82.1%)	8 (14.3%)	<0.001[a*]
Hematological	3 (10.7%)	0	0.034[b]
Neurological	22 (78.6%)	8 (14.3%)	<0.001[a*]
Neuropsychological	21 (75%)	24 (42.9%)	0.005[a]
Pulmonary	10 (35.7%)	8 (14.3%)	0.024[a]
Renal/genitourinary	10 (35.7%)	11 (19.6%)	0.109[a]
Skin/musculoskeletal	17 (60.7%)	12 (21.4%)	<0.001[a*]
Second malignancies	0	1 (1.8%)	1.000[b]

[*]Significance level (individual) = 0.004, Bonferroni adjustment for multiple comparisons, overall significance level 0.05
[a]Chi-squared test
[b]Fisher exact test

Figure 1. The total numbers all health conditions observed in brain tumor and other survivors by type of condition.

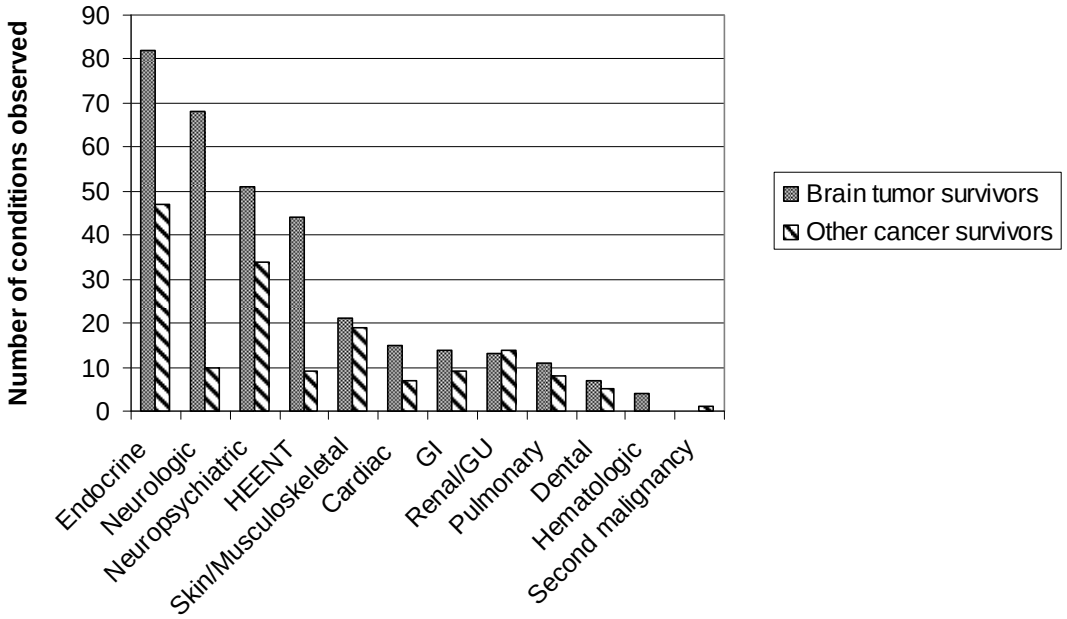

Figure 2. The distribution of the CTCAE severity scores of all health conditions observed.

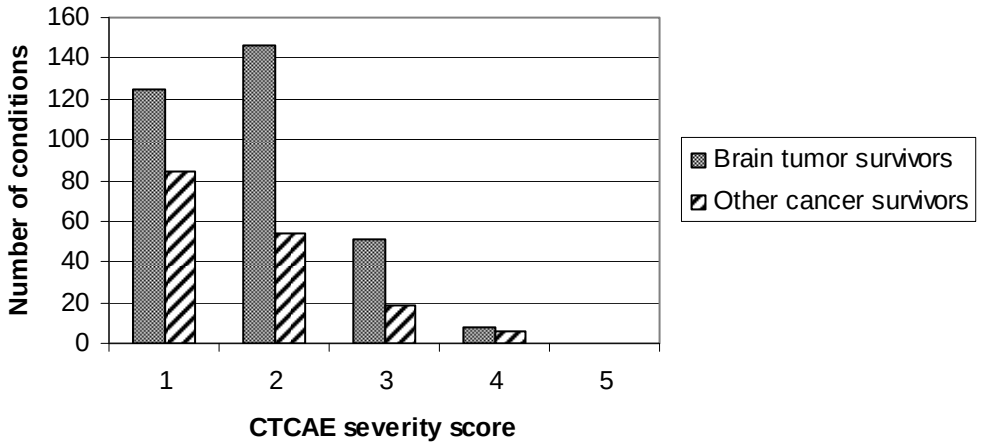

Figure 3. The distribution of maximum CTCAE severity scores by subject, comparing brain tumor and other survivors.

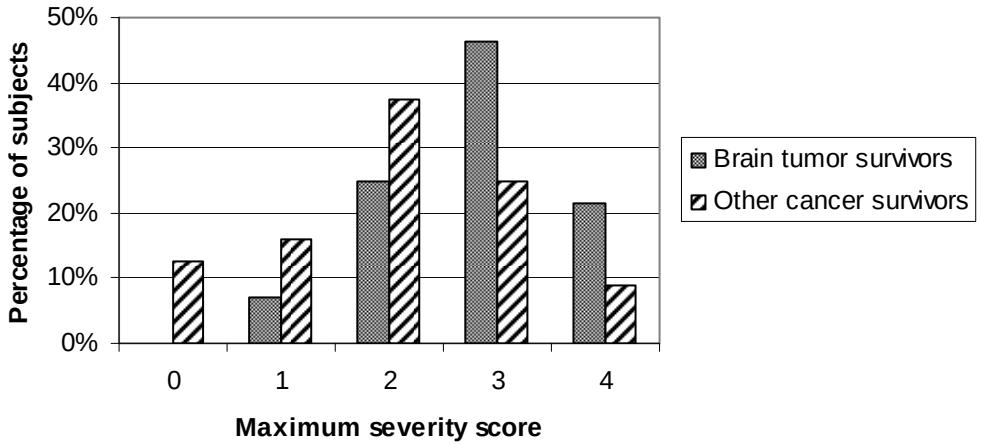

Table 6. Univariate and multivariate conditional logistic regression for the outcome of any grade 3 or grade 4 event for brain tumor and other cancer survivors.

Variable	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Diagnosis		0.002		0.046
Other survivors (n=28)	1		1	
Brain tumor (n=56)	4.57 (1.67, 12.51)		4.33 (1.03, 18.24)	
Radiation		0.560		0.528
No	1		1	
Yes	1.30 (0.54, 3.13)		0.69 (0.22, 2.16)	
Time between diagnosis and survivor visit				
≤5 yrs	1		1	
>5, ≤10 yrs	1.26 (0.38, 4.18)	0.708	0.82 (0.22, 3.15)	0.777
>10 yrs	11.48 (1.85, 71.37)	0.009	4.79 (0.65, 35.63)	0.126
Chemotherapy		0.218		0.792
No	1		1	
Yes	0.35 (0.06, 2.00)		1.33 (0.16, 11.07)	
Relapse		0.792	--	--
No	1			
Yes	0.85 (0.26, 2.83)			

For multivariable model: -2 log L= 63.83 , p-value for the LRT for full model 0.014

Table 7. Univariable and multiple linear regression for the outcome number of health conditions per survivor among brain tumor survivors.

Variable	Univariate			Multivariate (R^2= 0.41)	
	Parameter estimate	R-squared	p-value	Parameter estimate	p-value
Chemotherapy	3.48	0.08	0.140	3.15	0.105
Radiation	7.10	0.34	0.001	6.95	0.001
Age at diagnosis, yr	0.06	<0.01	0.792	--	--
Time between diagnosis and survivor visit, yr	0.07	<0.01	0.071	--	--
Relapse	2.67	0.06	0.226	--	--
Gender	-0.11	<0.01	0.959	--	--

Age at diagnosis and Time between diagnosis and survivor visit are continuous. All other predictors are dichotomous. Overall p-value for multivariate model 0.001.

Table 8. Univariable and multiple linear regression for the outcome number of endocrine conditions for brain tumor survivors.

Variable	**Univariate**			**Multivariate (R^2= 0.30)**	
	Parameter estimate	**R-squared**	**p-value**	**Parameter estimate**	**p-value**
Chemotherapy	0.24	<0.01	0.770	--	--
Radiation	1.57	0.15	0.045	1.81	0.015
Age at diagnosis, yr	-0.06	0.02	0.428	--	--
Time between diagnosis and survivor visit, yr	0.17	0.11	0.085	0.20	0.028
Relapse	0.81	0.05	0.276	--	--
Gender	0.06	<0.01	0.936	--	--

Age at diagnosis and Time between diagnosis and survivor visit is continuous. All other predictors are dichotomous. Overall p for multivariate model 0.012.