CCSS Concept Proposal

Project Title: First and **Recurren**t Stroke in Long-term Survivors of Childhood Cancer

Working Groups: Neuropsychology (Primary)
Chronic Disease
Neurology

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1. SPECIFIC AIMS

Stroke is a disabling consequence of childhood cancer—and childhood cancer treatment—that remains poorly understood. Prior studies have suggested that, among childhood cancer survivors, radiation therapy to the head and neck is a particularly strong predictor of stroke. The mechanism of stroke in these cases is likely a radiation arteriopathy, which can lead to artery-to-artery embolic infarcts, flow-related ischemia due to severe vessel stenosis or occlusion, or even hemorrhagic stroke due to rupture of fragile collateral vessels. However, many questions remain. The cumulative incidence of stroke in childhood cancer survivors has yet to be well established. Furthermore, among those with first stroke, rates and predictors of *recurrent* stroke have never been assessed. Other pediatric stroke data have suggested that children with an underlying arteriopathy have an extraordinarily high risk of recurrent stroke: 66% at 5 years. Children with radiation arteriopathy likely fall into this high risk category, but these pediatric stroke studies lacked sufficient numbers to analyze this subgroup. We need to better understand recurrent strokes in childhood cancer survivors to begin to develop rational strategies for secondary stroke prevention.

Our ultimate goal is to obtain external funding to answer these questions through a multicenter prospective cohort study. However, we feel that the current CCSS cohort can provide the critical data needed to justify such a study. Hence, we propose to study both first-stroke and recurrent stroke in survivors of childhood cancers that have been associated with long-term stroke risk: brain tumors, leukemia, and Hodgkin's disease.

Hypotheses: Survivors of childhood cancers--particularly those treated with head or neck radiation--are at increased risk of both first and recurrent stroke, and stroke leads to decreased quality of life in these patients.

Specific Aims:

1. To reassess the incidence and predictors of self-reported first-stroke in childhood cancer survivors (brain tumors, leukemia, and Hodgkin's disease) using the 2007 CCSS dataset, which has more stroke-related fields than prior datasets.
   Hypothesis: Radiation therapy to the head or neck increases the risk of stroke in survivors of childhood brain tumors, leukemia, and Hodgkin's disease.

2. To use existing CCSS data to determine whether cancer survivors with stroke have worse quality of life and higher mortality rates than those without stroke.
   Hypothesis: Incident first stroke worsens quality of life and mortality in childhood cancer survivors.

3. To perform a short mail survey of approximately 250 subjects with self-reported first stroke to determine rates and predictors of stroke *recurrence*.
   Hypotheses: The risk of recurrent stroke after first stroke in childhood cancer survivors is high. Prior radiation therapy to the head or neck and younger age at radiation therapy increase the risk of stroke recurrence.

The stroke recurrence aim is listed third only because of the logic that first strokes precede recurrent strokes; Aim 3 is actually of greatest interest to the investigators proposing this study. Data regarding recurrent stroke in childhood cancer survivors are lacking, and of critical importance to develop secondary stroke prevention strategies.

2. BACKGROUND

Stroke is a disabling consequence in long-term pediatric cancer survivors, particularly those with brain tumors, leukemia, and Hodgkin's disease since these types of cancer require head or neck radiation therapy (1, 2).

Radiation therapy is an integral part in the treatment of children with cancer, particularly in children with brain tumors. However, cranial radiation therapy (CRT) is associated with numerous long-term sequelae like e.g. cognitive decline, endocrine abnormalities as well as radiation-induced vasculopathies, especially in children of very young age. Early studies have shown that higher radiation dosages to the brain appear to be correlated with the incidence of radiation induced vasculopathy (3). In addition, children undergoing radiation therapy are also at higher risk to develop small lacunar infarcts at a median time of 2.01 years after radiation therapy, which is thought to be a consequence from radiation induced small vessel vasculopathy (4). Brain irradiation also appears to be associated with the development of a specific type of vasculopathy, known as progressive cerebral arterial occlusive disease or MoyaMoya syndrome (5). MoyaMoya syndrome is associated with ischemic as well as hemorrhagic strokes and often requires surgical bypass procedures. A study from the Children's Hospital in Boston found that 12/345 patients (3.5%) who were treated with radiation therapy for their underlying brain tumors, developed MoyaMoya syndrome (6). A recent study suggested an astonishingly high annual incidence rate of late-occurring strokes in childhood brain tumor survivors treated with CRT: 339.5 per 100,000 person years. Patients treated with CRT > 50 Gy were 3.3 times more likely to report a late occurring stroke then patients not receiving any radiation treatment (2). This incidence was 37-fold higher than cancer-free siblings after adjusting for age, race, and gender. This study was limited, however, in that stroke was defined by parental report, and not confirmed by medical record or imaging review. The mechanism of stroke in this setting is thought to be a radiation-induced arteriopathy. Although there are some existing data on risk factors for first-stroke and arteriopathy in children treated with CRT—namely optic pathway tumors associated with neurofibromatosis 1, younger age, and higher radiation dose to the circle of Willis—there are few data on the incidence of stroke confirmed by imaging analysis, mechanism of this arteriopathy, its natural history, and the rate and predictors of stroke *recurrence* in this setting (3,4,7). Hence, when faced with a child with a stroke due to radiation-induced arteriopathy, clinicians have little to offer either in terms of prognosis or treatment for secondary stroke prevention.

3. PRELIMINARY DATA

3.1. *Self-reported First Strokes in CCSS*. Bowers, et al, previously analyzed rates of self-reported late-occurring first-stroke in CCSS subjects with leukemia (n=4,828) and brain tumors (n=1,871) (2). Stroke was reported by 97 leukemia survivors, with an incidence of 58 per 100,000 person-years, and 117 brain tumor survivors, with an incidence of 268 per 100,000 person-years. Cumulative stroke incidence at 25 years was doubled in those treated with CRT: for leukemia survivors, 0.44% without CRT versus 0.84% with CRT; for brain tumor survivors, 2.85% without CRT versus 6.90% with CRT. In a separate analysis of 1,926 CCSS subjects with Hodgkin's disease, 24 reported a late-occurring stroke; all 24 had received mantle radiation (1). The stroke incidence was 84 per 100,000 person-years overall, and 110 per 100,000 person-years in those with mantle radiation.

These data suggest that the incidence of stroke in CCSS subjects is relatively high, and that we will have a large number of stroke outcomes for Aims 1 and 2. We would also anticipate that the number of stroke outcomes will increase for Aim 1, given the longer duration of follow-up at the time of the 2007 CCSS questionnaire. With regards to Aim 3, we will have at least **238 potential subjects** (97 with leukemia, 117 with brain tumors, and 24 with Hodgkins) for the survey of recurrent strokes. Again, the use of the 2007 CCSS dataset will likely increase the number of subjects with self-reported first-strokes. (Power calculations for Aim 3 are below, Section 4.3.)

3.2. *Stroke Recurrence Rates in Children with Arteriopathy: Results of the Kaiser Pediatric Stroke Study (KPSS)*.

KPSS (PI: H. Fullerton) is a population-based retrospective cohort study of childhood stroke. It utilized the cohort of all 2.4 million children (through 19 years of age) enrolled in a Northern Californian health maintenance organization between 1993 and 2003 (8). Potential cases were identified through electronic searches of inpatient, outpatient, and radiology databases, and confirmed through independent chart review by two child neurologists, with adjudication by a third. Vascular abnormalities were based on formal interpretations of clinical imaging abstracted by Dr. Fullerton. Arteriopathy was defined as any cerebral or cervical arterial stenosis, inclusive of specific entities such as moyamoya and arterial dissection. Isolated arterial occlusion was excluded from the definition as this can represent an embolic event, as opposed to intrinsic arterial disease. Among 97 cases of childhood arterial ischemic stroke (4 with a past medical history of childhood cancer: leukemia, lymphoma, pinealblastoma, and Wilm's tumor), the 5-year cumulative recurrence rate was 19%. As shown in the Kaplan-Meier curve (Figure 1), there were no recurrences among children with normal vascular imaging (solid line, n=30), while children with an arteriopathy (dashed line, n=22) had a 5-year cumulative recurrence rate of 66% (95% CI, 43-87%; p<0.0001 for the comparison).

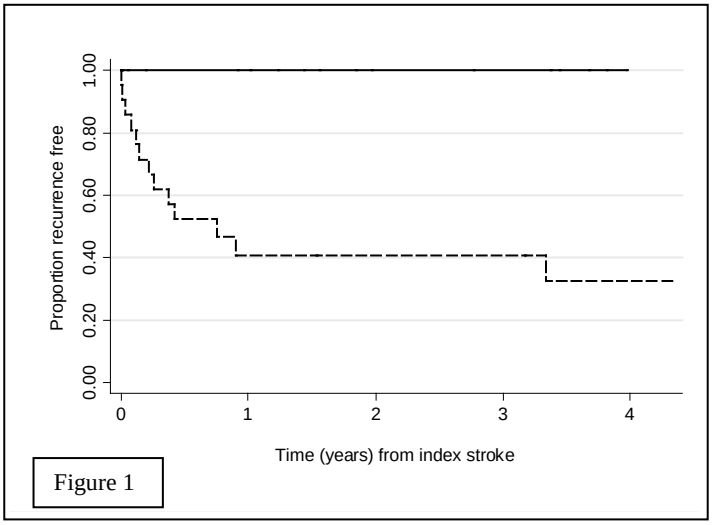

Figure 1

These data suggest that stroke recurrence rates are high in children with an underlying cerebral or cervical arteriopathy. Because a radiation-induced arteriopathy is the presumed mechanism of late-occurring stroke in childhood cancer survivors treated with cranial or mantle radiation, we anticipate finding a similarly high rate or recurrent stroke in Aim 3 of this study.

4. **METHODS**

The proposed study will focus on the CCSS subjects (1970-1986 cohort) with cancers commonly treated with radiation therapy to the head or neck: brain tumors (n=1,871), leukemia (n=4,828), and Hodgkin's lymphoma (n=1,926). This cohort includes only children who survived 5 years after cancer diagnosis. We propose to perform a secondary data analysis of existing CCSS data for Aims 1 and 2, and a follow-up mail survey of the 238 CCSS subjects with these cancers that have previously self-reported strokes. Depending on the robustness of the findings, we anticipate that these analyses could yield 2 to 3 manuscripts.

4.1. *Aim 1: To reassess the <u>incidence and predictors of self-reported first-stroke</u> in childhood cancer survivors (brain tumors, leukemia, and Hodgkins disease).*

This aim will replicate the prior analyses by Bowers, et al, (published 2005 & 2006) except that we will use the 2007 CCSS dataset, supplemented by the 2009 telephone stroke survey (1, 2). The advantages of this more recent dataset are (1) longer period of follow-up and (2) greater detail regarding the stroke event including motor and speech manifestations, and symptom duration lasting greater than 24 hours. In addition, the 2009 telephone stroke survey will attempt to confirm the self-reported strokes through telephone interview.

We would exclude from the analysis those subjects with stroke within the 1st 5 years from diagnosis (i.e., prior to inclusion in the cohort). The <u>primary outcome</u> will again be a dichotomous variable of "self-reported first stroke" (see Appendix 1, variable list). This variable will be based on data from the 2007 CCSS dataset, and will be defined as a self-reported first stroke with motor and/or speech manifestations, and duration greater than 24 hours. We will also use the 2009 telephone interview to create secondary dichotomous outcome variables of "interview-confirmed first stroke." This will be a self-reported first stroke, confirmed during the telephone interview, with signs and symptoms consistent with a stroke. <u>Predictors</u> will include cancer type (categorical), radiation treatment (dichotomous), and age at treatment. Age will be assessed both as a continuous and categorical variable. Additional exploratory predictors would include prior chemotherapy (particularly alkylator therapy and methotrexate), secondary tumors (as a dichotomous

variable), and tumor recurrence (prior to recurrent stroke). To account for variable duration of follow-up, we will use survival analysis techniques to calculate annualized and cumulative incidence rates (Table 3). The outcome will be time from 5-years-post-diagnosis (when they enter the cohort) to self-reported first stroke; subjects will be censored at death or loss to follow-up. We will assess whether age has a stronger impact on the hazard of stroke than time since cohort entry; if so, we will consider using age as the time scale for the survival analyses. To assess predictors of stroke, we will calculate univariate hazards ratios as a measure of relative risk using Cox Proportional Hazards techniques (Table 4). For predictors of interest, such as cancer type and prior radiation therapy, we will generate stratified cumulative incidence curves to create visual depictions of the detected effects of key factors (9). To determine independent predictors of stroke, we will create multivariate Cox Proportional Hazards models, using univariate screening with a p-value cut-off of 0.10 for inclusion in the model (Table 5). Using the results of the 2009 telephone survey, we will calculate the proportion of self-reported strokes from the 2007 survey that are confirmed through telephone interview. We will use that data to revise our estimates of the incidence of stroke in this cohort. If the number of subjects that participate in the telephone survey are sufficient, we will re-do these analyses using "interview-confirmed first stroke" as our outcome variable. However, we will have to compare baseline characteristics of interview participants to non-participants, and consider the volunteer bias that could be introduced into this analysis.

A limitation of this analysis is that only living subjects are contacted for the follow-up surveys; hence, the follow-up information will not capture strokes among subjects who died between questionnaires. For example, if they had a stroke after FU2003 and subsequently died, we will not have a way of capturing their stroke event. Although we will censor at loss-to-follow-up, this could lead to informative censoring. We will attempt to use death certificate cause of death data (from the 2009 NDI search) to make some adjustments by including cause of death info, but there will likely be an underestimation of the incidence of stroke, and stroke's impact on mortality (Aim 2). We will compare the baseline characteristics of those subjects included in the analysis versus those excluded because of death. The potential biases to the results will be carefully considered.

4.2. *Aim 2: To use existing CCSS data to determine whether cancer survivors with stroke have worse quality of life and higher mortality rates than those without stroke*.

This aim will also rely on existing data in the CCSS dataset. In particular, we will take advantage of quality of life measurements from 2003 using the SF-36 Health Survey (Table 7 describes baseline characteristics of this group). For mortality, we will use the most recent mortality data from the 2009 NDI search.

For these analyses, we will again include all children in the CCSS cohort with brain tumor, leukemia, or Hodgkins lymphoma. The primary predictor will be the dichotomous variable of "any self-reported stroke." We will exclude from the definition of this predictor any strokes that occurred *after* the measurement of the outcome variable. Outcomes will include mortality, perceptions of cognitive outcome (from FU2003 neurocognitive questionnaire [CCSS=NCQ]), quality of life as measured by the SF-36 Health Survey, and indirect measure of quality of life, such as level of education, marital status, etc. For the mortality analysis, we will use survival analysis techniques where the primary outcome is time from entry to cohort (5 years after diagnosis) to death, with censoring at loss to follow-up. The primary predictor ("any self-reported first stroke") will be treated as a time-varying covariate in Cox regression models. Because mortality will be affected by cancer type, we will analyze each subgroup separately. We will calculate cumulative mortality rates as well age and gender adjusted incidence rates and Standardized Mortality Ratios (SMRs) for subjects with versus without stroke (Table 6). Because stroke is a time-varying covariate, subjects with stroke will contribute person-time both before and after stroke.

For the other outcome variables, we will compare outcomes in the different cancer subgroups to determine whether or not they can be lumped (Table 8). We will generate summary statistics to compare these outcomes in subjects with versus without a history of stroke. We will use chi-square tests to compare categorical variables, such as marital status. We will compare continuous variables using Student's *t*-tests, if the data are normally distributed, or Mann-Whitney rank sum tests if they are not.

4.3. *Aim 3: To determine rates and predictors of stroke recurrence by performing a short mail survey of approximately 250 subjects with self-reported first stroke.*

This aim would include the subset of CCSS subjects (with brain tumor, leukemia, or Hodgkins lymphoma) with self-reported late-occurring first-strokes. As described above (Section 3.1), we would have at least 238 potential subjects for this aim. This sample size may be higher by using stroke self-report from the 2007 dataset which has a greater duration of follow-up, and hence will likely provide additional stroke cases. However, this may be mitigated by more deaths related to the longer follow-up period. These subjects would be surveyed regarding the occurrence and timing of any recurrent strokes (please see **Appendix 1; Note:** Dr. Les Robison has agreed to support the cost of mailing the survey to the 250 survivors who have previously reported a history of stroke. The mailing will be conducted through the CCSS Survey Center.). We will describe their baseline characteristics, including stroke risk factors and first stroke presentation, etiology, and treatment (Table 9). We will also describe the characteristics and etiology of the second stroke (Table 10).

We will again use survival analysis techniques to calculate cumulative incidence rates of stroke as well as age and gender adjusted recurrence rates per 100,000 person-years. The outcome will be time from first stroke (beyond 5 years from diagnosis) to first recurrence; subjects will be censored loss to follow-up and death will be treated as a competing risk event (Table 11). Potential predictors of recurrent stroke will include: cancer type, timing of first stroke (less than or greater than 10 years from cancer diagnosis), treatment with cranial or mantle radiation therapy, and age at radiation treatment. Additional predictors would include prior chemotherapy (particularly alkylator therapy and methotrexate), secondary tumors (as a dichotomous variable), and tumor recurrence (prior to recurrent stroke). To assess these predictors, we will generate stratified cumulative incidence curves and perform log-rank tests to determine the significance of any observed differences. We will also calculate hazards ratios as a measure of relative risk using Cox Proportional Hazards techniques (Table 12). To determine independent predictors of recurrent stroke, we will create multivariate Cox Proportional Hazards models, using univariate screening with a p-value cut-off of 0.10 for inclusion in the model (Table 13). We will consider the number of outcomes (recurrent strokes) as we decide how many predictors to include in our model. We will also perform stratified analyses to assess for potential interactions, such as chemotherapy modifying the association between radiation therapy and stroke recurrence.

Because it would also be of interest to determine whether first stroke during the first 5 years of diagnosis (prior to entry in the cohort) is a risk factor for recurrent stroke, we will also consider including in the survey study those CCSS subjects (with brain tumor, leukemia, or Hodgkins lymphoma) with self-reported early stroke (stroke within the first 5 years after diagnosis, prior to enrollment in CCSSHowever, we will first need to consider the potential bias introduced into this analysis by the difference in the way the first stroke was ascertained.

As described above, a limitation of this analysis will be that only living subjects will be available for the survey, and the subjects that were loss to follow-up due to death are likely to be different from those that survived to inclusion in the analysis. We will use data from the 2009 NDI search to assess which subjects from the original cohort have died. We will compare the baseline characteristics of those subjects from the original cohort that were included in the analysis to those who were not included.

Power Calculations: As described above (Preliminary Data, Section 3.1), we will have at least **238 potential subjects** (97 with leukemia, 117 with brain tumors, and 24 with Hodgkins) for the survey of recurrent strokes. Again, the use of the 2007 CCSS dataset may increase the number of subjects with self-reported first-strokes. However, disregarding these potential subjects, if one assumes a 25% loss to follow-up, and an additional non-response rate of 10% for subjects not lost to follow-up, we would still have a sample size of at least **160**. Based on our preliminary data from KPSS (Section 3.2), if we conservatively estimate an overall frequency of the primary outcome (recurrent stroke) of 25%, we would observe this outcome in 32 subjects. This should be an adequate sample size to calculate stroke recurrence rates with reasonably narrow confidence intervals (width of approximately ±7% from observed rate).

With regards to predictors of recurrent stroke, although we plan to perform survival analyses, we simplified our power calculations by basing them on a cohort study design with more uniform follow-up time. This simplifying assumption will likely underestimate the true power of the survival analyses. We based these calculations on the predictor of prior radiation treatment. If 50% of subjects with first stroke received radiation therapy, and the frequency of recurrent stroke is 10% in the unexposed group (no radiation) and 30% in the

exposed group, we would need a sample size of only 142 subjects to be powered at 80% to detect this difference (alpha set at 0.05).

5.0 FUTURE DIRECTIONS

In addition to the limitation discussed above regarding loss to follow-up, the proposed study will be limited by reliance on patient self-report of strokes, the retrospective nature of the stroke measurements, and the relatively small number of subjects with first stroke. It will leave many unanswered questions, with the most important one being how to prevent recurrent strokes in these childhood cancer survivors. The long-term goal is to use these data to design and obtain funding for a prospective study of recurrent stroke in long-term survivors of childhood cancer.

6.0 REFERENCES

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List of Appendices: **Page #**

Please note that both the variable list and tables may be more easily viewed in the original Excel file. They are difficult to read in this document due to small font size after pasting large tables into Word, but are provided here for a convenient overview.

The tables will be trimmed substantially for manuscript preparation, but this process will depend on the results. For example, if the three cancer groups (brain tumor, leukemia, Hodgkin’s) share similar results, we will be able to lump them for the manuscript.

Appendix 1: **CCSS STROKE SURVEY**

Cover Letter for Stroke Survey

Dear ___,

Thank you again for your participation in the Childhood Cancer Survivor Study. We are now trying to learn more about strokes that occur in survivors like you.

Stroke is when a part of the brain is injured because a blood vessel to the brain is either blocked or bursts. When that happens, part of the brain cannot receive oxygen or nutrients. There are 2 types of stroke: ischemic stroke, when blood flow through a vessel to the brain is blocked, such as by a clot; and hemorrhagic stroke, when a blood vessel in the brain ruptures, causing bleeding into the brain. Strokes often present with the sudden loss of a particular body function: weakness or numbness on one side of the body, drooping of one side of the face, difficulty speaking, or loss of coordination ("ataxia"). People who have been treated for a childhood cancer—especially brain tumors, leukemia, and Hodgkins disease—appear to be more likely to have a stroke. Our prior surveys indicate that you had a stroke in the past. We would like to find out more about your stroke, and whether you had more than one stroke.

Our prior surveys indicate that you had previously been told by a physician that you had had a stroke. Is this correct?
[ ] yes, I had a stroke [ ] no, I never had a stroke

If no, please return the survey; you do not need to answer any more questions, but we thank you for your time in responding. If yes, please proceed.

CCSS Stroke Survey

1) Radiation therapy as a treatment for cancer can injure normal blood vessels, sometimes in a delayed fashion. This sometimes is called "radiation arteritis" or "radiation vasculopathy." Have you ever been told that you had **radiation injury** to a blood vessel(s) to the brain? [ ] yes [ ] no
2) If yes, did you ever receive any sort of treatment for this radiation injury? (check all that apply)
   [ ] steroid treatment (for example, prednisone or solumedrol) [ ] hyperbaric oxygen therapy [ ] other(?)
3) Have you ever been told that you have **moyamoya** (a condition of narrowing of blood vessels to the brain)? (Moyamoya can be the result of particularly severe radiation injury, so it is okay to answer "yes" to both this question and question 1.) [ ] yes [ ] no
4) If yes, have you ever had a **surgery** for moyamoya to improve blood flow to the brain? (These might be called an "onlay procedure" or "EDAS" or "direct bypass" or "STA-MCA bypass.")
   [ ] yes [ ] no [ ] not sure How old were you when the first surgery was performed? ___ years
5) Have you ever been told that you have a **vascular malformation** in the brain? [ ] yes [ ] no
6) If yes, what type of vascular malformation? [ ] cavernous malformation, also known as a "cav mal," "cavernous hemangioma," or "occult vascular malformation" [ ] arteriovenous malformation (AVM)[ ] I don't know
7) Do you have a diagnosis of **neurofibromatosis type I** (NF-I)? [ ] yes [ ] no

First Stroke

We would like to ask you more details about the **first stroke** that you had.

8) How old were you when you had your first stroke? ____ years
9) Did you have any sort of **head imaging (CT or MRI)** that showed your stroke? [ ] yes [ ] no, imaging was done, but did not show the stroke [ ] no, head imaging was never done [ ] I don't know
10) Did you have a **hemorrhagic** stroke (bleeding into the brain) or an **ischemic** stroke (blockage of a blood vessel to the brain)? [ ] hemorrhagic stroke [ ] ischemic stroke [ ] I don't know
11) What sort of **symptoms** did you have? (check all that apply) [ ] weakness on one side of the body [ ] weakness on both sides of the body [ ] difficulty speaking [ ] difficulty walking [ ] vertigo (dizziness where it seems like the room is spinning, or the floor is moving) [ ] numbness on one side of the body [ ] numbness on both sides of the body [ ] seizure/convulsion [ ] headache [ ] no symptoms, it was a "silent stroke"
12) Did your symptoms last for greater than 24 hours? [ ] yes [ ] no
13) Did you receive any **medical treatment** for your stroke while in the **hospital**? [ ] blood thinning with aspirin [ ] blood thinning with heparin, Lovenox, Enoxaparin, Coumadin, or warfarin [ ] blood thinning, but I don't recall what type [ ] no [ ] I do not recall
14) Did you receive any **medical treatment** for your stroke at **home** (after discharge from the hospital)? [ ] blood thinning with aspirin [ ] blood thinning with heparin, Lovenox, Enoxaparin, Coumadin, or warfarin [ ] blood thinning, but I don't recall what type [ ] no [ ] I do not recall
15) Did you **recover** from your first stroke? [ ] yes, I had a complete recovery [ ] yes, I had a partial recovery (not back to the way I was before) [ ] no, I had no recovery

Recurrent Strokes

We would now like to ask you about any **recurrent** strokes you may have had.

16) Have you ever been told by a physician that you had had a second (recurrent) stroke?[ ] yes [ ] no
    If no, please return the survey; you do not need to answer any more questions. If yes, please proceed.
17) How old were you when you had the second stroke? ____ years
18) Did you have any sort of **head imaging (CT or MRI)** that showed your second stroke? [ ] yes [ ] no, imaging was done, but did not show the stroke [ ] no, head imaging was never done [ ] I don't know
19) Did you have a **hemorrhagic** stroke (bleeding into the brain) or an **ischemic** stroke (blockage of a blood vessel to the brain)? [ ] hemorrhagic stroke [ ] ischemic stroke [ ] I don't know
20) What sort of **symptoms** did you have with this second stroke? (check all that apply) [ ] weakness on one side of the body [ ] weakness on both sides of the body [ ] difficulty speaking [ ] difficulty walking [ ] vertigo (dizziness where it seems like the room is spinning, or the floor is moving) [ ] numbness on one side of the body [ ] numbness on both sides of the body [ ] seizure/convulsion [ ] headache
21) Did your symptoms last for greater than 24 hours? [ ] yes [ ] no
22) Were you taking any **blood thinners** at the time of your second stroke?

[ ] blood thinning with aspirin [ ] blood thinning with heparin, Lovenox, Enoxaparin, Coumadin, or warfarin [ ] blood thinning, but I don't recall what type [ ] no [ ] I do not recall

23) Did you **recover** from your second stroke? [ ] yes, I had a complete recovery [ ] yes, I had a partial recovery (not back to the way I was before) [ ] no, I had no recovery
24) How many strokes do you believe you have had in total? [ ] 2 [ ] 3 [ ] 4 [ ] >4
25) Do you feel that your strokes affected your **quality of life**? [ ] No [ ] Yes, it decreased my quality of life somewhat [ ] Yes, it decreased my quality of life a lot

Variable List

Note: for all variables, missing data will be represented as "."; dichotomous variables will be binary (0=no, 1=yes)

Aim	Variable Name (or cateogry name)	Form	Question #	Var Type	Definition
SA1: Outcome Variables					
	Any 1st stroke 2007	f/u 2007	K14	dichot	=1 if "yes" to question K14 AND age at stroke minus age at cancer diagnosis is > 5 years
	Self-reported 1st stroke 2007	f/u 2007	K14 a, b, d, e, f	dichot	Any 1st stroke=1 AND "yes" to duration>24 hours (K14 a), AND "yes" to either motor deficits or speech deficits (K14 b, d, e, or f)
	Interview confirmed 1st stroke 2009	tel 2009		dichot	endorsed stroke and signs/symptoms consistent with stroke
SA1 & 3: Predictor Variables					
	Sex, female	Baseline	A2	dichot	
	Race	Baseline		categorical	
	Age at cancer diagnosis	?	?	continuous	Age at initial cancer diagnosis, in years
	(Cancer diagnosis)				
	Brain tumor			dichot	
	Leukemia			dichot	
	Hodgkin's			dichot	
	Tumor recurrence			dichot	yes/no, tumor recurrence that required treatment
	Secondary tumor			dichot	yes/no, secondary tumor
	Vital Status, alive, 2007	f/u 2007	?	dichot	=1 if alive in 2007
	Age at 2007 questionnaire	f/u 2007	"today's date"	continuous	=year of birth minus year of completion of form, expressed in years
	(Treatment; Tables 1 & 3)				RT=radiation therapy; data in Bowers et al 2006, but could not find on on-line forms from CCSS website
	Radiation, any	MR abstr	page 10	dichot	yes/no, from medical record abstraction form, page 10
	Cranial RT	?	?	dichot	yes no, received cranial radiation therapy prior to 2007
	Cranial RT dose, Gy	?	?	continuous	total dose of cranial RT
	Mantle RT	?	?	dichot	yes/no, received mantle radiation therapy prior to 2007
	Mantle RT dose, Gy	?	?	continuous	total dose of mantle RT
	Chemotx, alkylating agent	?	?	dichot	yes/no, received this form of chemotx prior to 2007
	Chemotx, methotrexate	?	?	dichot	yes/no, received this form of chemotx prior to 2007
	Chemotx, other	?	?	dichot	yes/no, received this form of chemotx prior to 2007
SA1: Stroke Characteristics					
	Age at 1st stroke	f/u 2007	K14	continuous	age at first stroke, in years
	Time from cancer dx to 1st stroke	f/u 2007	K14	continuous	=age at 1st stroke minus age at cancer diagnosis, in years
	Deficits > 24 hours, 1st stroke	f/u 2007	K14 a	dichot	=1 if "yes" to "did the symptoms last more than 24 hours"
	Deficits present at 2007 f/u	f/u 2007	K14	dichot	=1 if "yes, and the condition is still present" to either motor or speech deficits (K14 b, d, e, f)
	(Symptoms at initial presentation)				for all, =1 if "yes, and condition still present" OR "yes, but condition no longer present"
	Speech deficit	f/u 2007	K14 b	dichot	=1 if "yes" to "speech"
	Unilateral deficit	f/u 2007	K14 b	dichot	=1 if "yes" to "only one side of body"
	Bilateral deficit	f/u 2007	K14 b	dichot	=1 if "yes" to "both sides of body"
	Arm weakness	f/u 2007	K14 d	dichot	
	Leg weakness	f/u 2007	K14 e	dichot	
	Paralysis of any kind	f/u 2007	K14 f	dichot	

Continued on next page

SA2: Predictor Variables					
	Any 1st stroke (2000)	f/u 2000	p.10, 10 g	dichot	=1 if "yes" to question K14 AND age at stroke minus age at cancer diagnosis is > 5 years
SA2: Outcome Variables					
	QOL score (SF36), mean (SD)	f/u 2003			quality of life score from SF36 quesionnaire
	Physical function			continuous	
	Physical role			continuous	
	Bodily pain			continuous	
	General health			continuous	
	Vitality			continuous	
	Emotional role			continuous	
	Social function			continuous	
	Mental health			continuous	
	Physical component summary			continuous	
	Mental component summary			continuous	
	Neurocognitive outcome, CCS-NCQ	f/u 2003			Neurocognitive questionnaire (NCQ) scores
	Task efficiency			continuous	
	Emotional regulation			continuous	
	Organization			continuous	
	Memory			continuous	
	Vital Status, alive, 2009	NDI	?	dichot	=1 if alive as of 2009 NDI search
	Married (Q2)	f/u 2003	2	dichot	=1 if checked "married" or "living with partner as married"
	Divorced/separated (Q2)	f/u 2003	2	dichot	=1 if checked "divorced" or "separated or no longer living as married"
	Living with parents/sibs/relative (Q3)	f/u 2003	3	dichot	=1 if checked living with parents, brother/sister, AND/OR other relatives
	Employment status (Q4)	f/u 2003	4	categorical	3 categories: employed (full or part time, or working in home), unemployed (seeking work), or unable to work due to illness/disability
	(Level of education, Q1)				Variables are not mutually exclusive
	Less than 12 years (high school)	f/u 2003	1	dichot	=1 if checked 1-8 years or 9-12 years (high school) but did not graduate
	High school graduate or above	f/u 2003	1	dichot	=1 if checked completed high school/GED OR training after HS, college (any), or post-graduate
	College gratduate or above	f/u 2003	1	dichot	=1 if checked college graduate or post-graduate
	Post graduate	f/u 2003	1	dichot	=1 if checked post-graduate

Continued on next page

SA3: Outcome variable					
	Recurrent stroke	f/u 2009	21		
	Age at 2nd stroke	f/u 2009	22	continuous	age at 2nd stroke, in years
	Time from cancer dx to 2nd stroke	f/u 2009		continuous	=age at 2nd stroke minus age at cancer diagnosis, in years
SA3: Stroke predictors and characteristics					
Will use the same predictors used for SA1, as well as the ones below:					
	Radiation arteritis	f/u 2009		dichot	
	Radiation arteritis treatment	f/u 2009		dichot	
	Steroids	f/u 2009		dichot	
	Hyperbaric oxygen	f/u 2009		dichot	
	Unknown	f/u 2009		dichot	
	Age at treatment of radiation arteritis	f/u 2009		continuous	age at treatment of radiation arteritis, years
	Moyamoya	f/u 2009		dichot	
	Moyamoya surgery	f/u 2009		dichot	
	bypass surgery	f/u 2009		dichot	yes, no, or missing (unknown)
	Age at surgery	f/u 2009		continuous	age at moyamoya surgery, years
	Vascular malformation	f/u 2009		dichot	
	Vascular malformation type	f/u 2009		categorical	4 categories: none (0), cavernous malformation (cav mal), AVM, vascular malform of unknown type
	History of NF-1	f/u 2009		dichot	
	Age at first stroke	f/u 2009		continuous	
	Interval from diagnosis to 1st stroke	f/u 2009		dichot	age at 1st stroke minus age at cancer diagnosis, years
	Interval from RT to 1st stroke	f/u 2009		dichot	age at 1st stroke minus age at radiation therapy, years
	(Characteristics of 1st stroke)				
	Symptom duration > 24 hours	f/u 2009		dichot	
	Unilateral weakness	f/u 2009		dichot	
	Bilateral weakness	f/u 2009		dichot	
	Abnormal speech	f/u 2009		dichot	
	Abnormal gait	f/u 2009		dichot	
	Vertigo	f/u 2009		dichot	
	Unilateral numbness	f/u 2009		dichot	
	Bilateral numbness	f/u 2009		dichot	
	Seizure at the time of stroke	f/u 2009		dichot	
	Headache at the time of stroke	f/u 2009		dichot	
	No symptoms ("silent stroke")	f/u 2009		dichot	
	(Confirmation of 1st stroke by imaging)	f/u 2009			
	CT/MRI confirmation			dichot	
	No, imaging done, no infarct			dichot	
	No, no imaging done			dichot	
	Unknown			dichot	
	First stroke type	f/u 2009		categorical	3 categories: hemorrhagic, ischemic, unknown
	Recovery from 1st stroke	f/u 2009		categorical	3 categories: complete, partial, no recovery
	Antithrombotics in hospital	f/u 2009		categorical	4 categories: none, aspirin, anti-coagulation (heparin/coumadin), anti-thrombotic (type unknown)
	Antithrombotics at home	f/u 2009		categorical	4 categories: none, aspirin, anti-coagulation (heparin/coumadin), anti-thrombotic (type unknown)
	Age at second stroke	f/u 2009		continuous	years
	Interval from 1st to 2nd stroke	f/u 2009		continuous	convert all responses to calendar years
	(Characteristics of 2nd stroke)				
	Symptom duration > 24 hours	f/u 2009		dichot	
	Unilateral weakness	f/u 2009		dichot	
	Bilateral weakness	f/u 2009		dichot	
	Abnormal speech	f/u 2009		dichot	
	Abnormal gait	f/u 2009		dichot	
	Vertigo	f/u 2009		dichot	
	Unilateral numbness	f/u 2009		dichot	
	Bilateral numbness	f/u 2009		dichot	
	Seizure at the time of stroke	f/u 2009		dichot	
	Headache at the time of stroke	f/u 2009		dichot	
	No symptoms ("silent stroke")	f/u 2009		dichot	
	(Confirmation of 2nd stroke by imaging)	f/u 2009			
	CT/MRI confirmation			dichot	
	No, imaging done, no infarct			dichot	
	No, no imaging done			dichot	
	Unknown			dichot	
	Second stroke type	f/u 2009		categorical	3 categories: hemorrhagic, ischemic, unknown
	Recovery from 2nd stroke	f/u 2009		categorical	3 categories: complete, partial, no recovery
	Antithrombotics at the time of recurrentce	f/u 2009		categorical	4 categories: none, aspirin, anti-coagulation (heparin/coumadin), anti-thrombotic (type unknown)
	Total number of strokes	f/u 2009		categorical	4 categories: 2, 3, 4, >4 (if no recurrence, then ".")
	Decreased QOL	f/u 2009		categorical	3 categories: no, somewhat decreased, very decreased

Appendix 3: Tables

Table 1. Baseline characteristics of childhood cancer survivors and siblings participating in the 2007 follow-up survey

	Childhood Cancer Survivors											
	A		B		C		D		E			
	Brain Tumor		Leukemia		Hodgkins		Any cancer		Siblings		p-value	p-value
	N=		N=		N=		N=		N=		(A vs B vs C)	(D vs E)
Characteristic	No.	%	No.	%	No.	%	No.	%	No.	%		
Vital status												
Alive												
Dead												
Sex												
Male												
Female												
Race												
White, non-Hispanic												
Black												
Hispanic												
Other												
Age at 2007 survey, y, mean (SD)												
Age at cancer diagnosis, y, mean (SD)												
Interval from diagnosis to survey, y, mean (SD)												
Cancer diagnosis												
Brain tumor												
Leukemia												
Hodgkin's												
Treatment												
No radiation therapy (RT)												
RT, any												
Cranial RT (dichotomous)												
Cranial RT dose, Gy, mean (SD)*												
Mantle RT (dichotomous)												
Mantle RT dose, Gy, mean (SD)*												
Age at RT, years, mean (SD)*												
Age at RT (categorical)												
0-4.9 years												
5-9.9 years												
10-14.9 years												
15-20 years												

*or median (IQR) if not normally distributed

Table 2. Characteristics of first stroke in childhood cancer survivors and sibling controls participating in the 2007 follow-up survey with any self-reported first stroke (exluding strokes occurring within 1st 5 years of cancer diagnosis)

	Childhood Cancer Survivors											
	A		B		C		D		E			
	Brain Tumor		Leukemia		Hodgkins		Any cancer		Siblings		p-value	p-value
	N=		N=		N=		N=		N=		(A vs B vs C)	(D vs E)
Characteristic	No.	%	No.	%	No.	%	No.	%	No.	%		
Age at 1st stroke, y, median (range)												
Time from cancer dx to 1st stroke, y, median (range)									--	--		--
Deficits > 24 hours												
Deficits present at 2007 questionnaire												
Symptoms at initial presentation												
Speech deficit												
Unilateral motor deficit												
Bilateral motor deficit												
Arm weakness												
Leg weakness												
Paralysis of any kind												
Treatment												
Radiation, any									--	--		--
Cranial RT (dichotomous)									--	--		--
Cranial RT dose, Gy, mean (SD)*									--	--		--
Mantle RT (dichotomous)									--	--		--
Mantle RT dose, Gy, mean (SD)*									--	--		--
Chemotx, alkylating agent									--	--		--
Chemotx, methotrexate									--	--		--
Chemotx, other									--	--		--

Table 3A. Incidence of **any** late-occurring stroke among childhood cancer survivors in the 2007 follow-up study, stratified by cancer type and radiation therapy, and siblings. Relative risk compared to siblings (hazard ratio)

			Incidence, per 100,000 person-years						
			Cumulative Incidence						
Group	Total No.	No. w/ Stroke	5 year	10 year	20 year	Average annual	HR	95% CI	p-value
Siblings							Ref		
All Cancer Survivors									
Brain tumor									
With RT									
Without RT									
Leukemia									
With RT									
Without RT									
Hodgkins									
With RT									
Without RT									

RT=prior cranial radiation therapy or prior mantle radiation therapy

Table 3B. Incidence of **clinically significant** late-occurring stroke among childhood cancer survivors, stratified by cancer type and radiation therapy, and siblings. Relative risk compared to siblings (hazard ratio)

			Incidence, per 100,000 person-years						
			Cumulative Incidence						
Group	Total No.	No. w/ Stroke	5 year	10 year	20 year	Average annual	HR	95% CI	p-value
Siblings							Ref		
All Cancer Survivors									
Brain tumor									
With RT									
Without RT									
Leukemia									
With RT									
Without RT									
Hodgkins									
With RT									
Without RT									

RT=prior cranial radiation therapy or prior mantle radiation therapy

NOTE:
Table A is "any 1st stroke" and Table B is "clinically significant 1st stroke"

Table 4. Univariate predictors of first-stroke among CCSS survivors that completed follow-up questionnaire 2007, stratified by any self-reported first-stroke (exluding strokes occurring within 1st 5 years of cancer diagnosis)

		Stroke§ n=xxx		No Stroke n=xxx				
Characteristic		No.	%	No.	%	HR	95% CI	p-value
Sex								
	Male					Ref.		
	Female							
Race								
	White, non-Hispanic					Ref.		
	Black							
	Hispanic							
	Other							
Age at cancer diagnosis								
	0-4.9 years					Ref.		
	5-9.9 years							
	10-14.9 years							
	15-20 years							
Cancer diagnosis								
	Brain tumor					Ref.		
	Leukemia							
	Hodgkin's							
Radiation Treatment								
	No radiation therapy (RT)					Ref.		
	RT, any							
	Any cranial RT							
	Cranial RT dose>xx Gy							
	Mantle RT							
	Mantle RT dose >35 Gy							
Chemotherapy								
	No chemotherapy					Ref.		
	Chemotx, alkylating agent							
	Chemotx, methotrexate							
	Chemotx, other							
Recurrent or secondary tumor								
	Recurrent tumor (requiring tx)							
	Secondary malignancy							
Age at RT, years, mean (SD)*								
Age at RT (categorical)								
	0-4.9 years					Ref.		
	5-9.9 years							
	10-14.9 years							
	15-20 years							

§ any self-reported 1st stroke, based on 2007 questionnaire, occurring at least 5 years after stroke diagnossis

RT=radiation therapy

*or median (IQR) if not normally distributed

HR=hazards ratio from univariate Cox proportional hazards models

Table 5. Independent predictors of any self-reported first stroke (excluding strokes within first 5 years of diagnosis) among CCSS survivors that completed follow-up questionnaire 2007

Variables will depend on results of univariate analysis

Predictor		HR	95% CI	p-value
Sex				
	Male	Ref.		
	Female			
Race				
	White, non-Hispanic	Ref.		
	Black			
	Hispanic			
	Other			
Cancer diagnosis				
	Brain tumor	Ref.		
	Leukemia			
	Hodgkin's			
Radiation Treatment		Ref.		
	No radiation therapy (RT)			
	RT, any			
	Any cranial RT			
	Cranial RT dose>xx Gy			
	Mantle RT			
	Mantle RT dose >35 Gy			
Chemotherapy		Ref.		
	No chemotherapy			
	Chemotx, alkylating agent			
	Chemotx, methotrexate			
	Chemotx, other			
Recurrent or secondary tumor				
	Recurrent tumor (requiring tx)			
	Secondary malignancy			
Age at RT, years, mean (SD)*				
Age at RT (categorical)		Ref.		
	0-4.9 years			
	5-9.9 years			
	10-14.9 years			
	15-20 years			

RT=radiation therapy

*or median (IQR) if not normally distributed

HR=hazards ratio from univariate Cox proportional hazards models

Table 6. Stroke as a predictor of mortality after cancer diagnosis in childhood cancer surviviors participating in the 2007 follow-up survey

			Cumulative Mortality (%)								
Cancer type	Stroke status	No.	5 year	10 year	20 year	HR	95% CI	p-value	SMR	95% CI	p-value
Brain tumor	No stroke					Ref.					
	Stroke										
Leukemia	No stroke					Ref.					
	Stroke										
Hodgkins	No stroke					Ref.					
	Stroke										
Any cancer	No stroke					Ref.					
	Stroke										

SMR=standardized mortality ratio; age and sex standardized according to the US mortality rates from the NCHS

Table 7. Baseline characteristics of childhood cancer survivors participating in the 2003 follow-up survey

	A Brain Tumor		B Leukemia		C Hodgkins		D Any cancer		p-value
	N=		N=		N=		N=		(A vs B vs C)
Characteristic	No.	%	No.	%	No.	%	No.	%	
Vital status									
Alive									
Dead									
Sex									
Male									
Female									
Race									
White, non-Hispanic									
Black									
Hispanic									
Other									
Age at 2007 survey, y, mean (SD)									
Age at cancer diagnosis, y, mean (SD)									
Interval from diagnosis to survey, y, mean (SD)									
Cancer diagnosis									
Brain tumor									
Leukemia									
Hodgkin's									
Treatment									
No radiation therapy (RT)									
RT, any									
Cranial RT (dichotomous)									
Cranial RT dose, Gy, mean (SD)*									
Mantle RT (dichotomous)									
Mantle RT dose, Gy, mean (SD)*									
Age at RT, years, mean (SD)*									
Age at RT (categorical)									
0-4.9 years									
5-9.9 years									
10-14.9 years									
15-20 years									

*or median (IQR) if not normally distributed

Table 8. Quality of life (QOL) in childhood cancer survivors participating in the 2003 follow-up survey, stratifed by cancer type and any self-reported stroke in **2003** (patients deceased by 2003 are excluded)

	Brain Tumors					Leukemia					Hodgkins					All Cancers				
	With Stroke		Without stroke			With Stroke		Without stroke			With Stroke		Without stroke			With Stroke		Without stroke		
	N=		N=			N=		N=			N=		N=			N=		N=		
Variable	No.	%	No.	%	p-value	No.	%	No.	%	p-value	No.	%	No.	%	p-value	No.	%	No.	%	p-value
QOL score (SF36), mean (SD)																				
Physical function																				
Physical role																				
Bodily pain																				
General health																				
Vitality																				
Emotional role																				
Social function																				
Mental health																				
Physical component summary																				
Mental component summary																				
Neurocognitive outcome score, mean (SD)																				
Task efficiency																				
Emotional regulation																				
Organization																				
Memory																				
Married (Q2)																				
Divorced or separated (Q2)																				
Living with parents/sibs/relative (Q3)																				
Employment status (Q4)																				
Employed (full/part/or in home)																				
Unemployed (seeking work)																				
Unable to work due to disability																				
Level of education (Q1)																				
Less than 12 years (high school)																				
High school graduate or above																				
College gratduate or above																				
Post graduate																				

Table 9. Baseline characteristics of childhood cancer survivors with previously self-reported first-stroke participating in the 2009 follow-up survey

	A		B		C		D		
	Brain Tumor		Leukemia		Hodgkins		Any cancer		p-value
	N=		N=		N=		N=		(A vs B vs C)
Characteristic	No.	%	No.	%	No.	%	No.	%	
Vital status at time of 2009 survey, alive									
Sex, male									
Race									
White, non-Hispanic									
Black									
Hispanic									
Other									
Age at 2009 survey, y, mean (SD)									
Age at cancer diagnosis, y, mean (SD)									
Interval from diagnosis to survey, y, mean (SD)									
Treatment									
No radiation therapy (RT)									
RT, any									
Cranial RT (dichotomous)									
Cranial RT dose, Gy, mean (SD)*									
Mantle RT (dichotomous)									
Mantle RT dose, Gy, mean (SD)*									
Age at RT, years, mean (SD)*									
Age at RT (categorical)									
0-4.9 years									
5-9.9 years									
10-14.9 years									
15-20 years									
History of NF-1									
Radiation arteritis									
Radiation arteritis treatment									
Steroids									
Hyperbaric oxygen									
Unknown									
Moyamoya									
Moyamoya treatment									
Bypass procedure									
Age at bypass, y, median (IQR)									
Cavernous malformation									
Arteriovenous malformation									
Vascular malformation, other or unknown									
Age at first stroke, y, mean (SD)*									
Interval from diagnosis to 1st stroke, y, mean (SD)*									
Interval from RT to 1st stroke, y, mean (SD)*									
Characteristics of 1st stroke									
Symptom duration > 24 hours									
Unilateral weakness									
Bilateral weakness									
Abnormal speech									
Abnormal gait									
Vertigo									
Unilateral numbness									
Bilateral numbness									
Seizure at the time of stroke									
Headache at the time of stroke									
No symptoms ("silent stroke")									
Confirmation of 1st stroke by imaging									
CT or MRI confirmation									
Recovery from 1st stroke									
Complete									
Partial									
No recovery									
*or median (IQR) if not normally distributed									

Table 10. Characteristics of recurrent stroke in childhood cancer survivors participating in the 2009 follow-up survey with any self-reported first stroke (exluding strokes occurring within 1st 5 years of cancer diagnosis)

	Childhood Cancer Survivors								
	A		B		C		D		
	Brain Tumor		Leukemia		Hodgkins		Any cancer		p-value
	N=		N=		N=		N=		(A vs B vs C)
Characteristic	No.	%	No.	%	No.	%	No.	%	
Time from 1st stroke to 2nd stroke, y, median (range)									
Characteristics of 2nd stroke									
Symptom duration > 24 hours									
Unilateral weakness									
Bilateral weakness									
Abnormal speech									
Abnormal gait									
Vertigo									
Unilateral numbness									
Bilateral numbness									
Seizure at the time of stroke									
Headache at the time of stroke									
No symptoms ("silent stroke")									
Confirmation of 2nd stroke by imaging									
CT or MRI confirmation									
Recovery from 2nd stroke									
Complete									
Partial									
No recovery									
More than 1 recurrence (dichotomous)									
Total number of strokes, median (range)									
Strokes have decreased quality of life (dichotomous)									

Table 11. Incidence of **recurrent** stroke among childhood cancer survivors with self-reported first strokes, participating in the 2009 survey, stratified by cancer type and radiation therapy, and siblings. Relative risk compared to siblings (hazard ratio)

Group	Total No.	No. w/ Stroke	Cumulative Incidence (%) 5 year	10 year	20 year	Average annual	HR	95% CI	p-value
Siblings							Ref		
All Cancer Survivors									
Brain tumor									
With RT									
Without RT									
Leukemia									
With RT									
Without RT									
Hodgkins									
With RT									
Without RT									

RT=prior cranial radiation therapy or prior mantle radiation therapy

Table 12. Univariate predictors of recurrent stroke among CCSS survivors with previously reported first-strokes

	Recurrence§ n=xxx		No Recurrence n=xxx				
Characteristic	No.	%	No.	%	HR	95% CI	p-value
Sex							
Male					Ref.		
Female							
Race							
White, non-Hispanic					Ref.		
Black							
Hispanic							
Other							
Age at cancer diagnosis							
0-4.9 years					Ref.		
5-9.9 years							
10-14.9 years							
15-20 years							
Cancer diagnosis							
Brain tumor					Ref.		
Leukemia							
Hodgkin's							
Radiation Treatment							
No radiation therapy (RT)					Ref.		
RT, any							
Any cranial RT							
Cranial RT dose>xx Gy							
Mantle RT							
Mantle RT dose >35 Gy							
Chemotherapy							
No chemotherapy					Ref.		
Chemotx, alkylating agent							
Chemotx, methotrexate							
Chemotx, other							
Recurrent or secondary tumor							
Recurrent tumor (requiring tx)							
Secondary malignancy							
Age at RT, years, mean (SD)*							
Age at RT (categorical)							
0-4.9 years					Ref.		
5-9.9 years							
10-14.9 years							
15-20 years							
Age at 1st stroke, years, mean (SD)*							
Age at 1st stroke (categorical)							
0-4.9 years							
5-9.9 years							
10-14.9 years							
15-19.9 years							
20-29.9 years							
30-39.9 years							
Interval from RT to 1st stroke, y, mean (SD)*							
Interval from RT to 1st stroke (categorical)							
0-4.9 years							
5-9.9 years							
10-14.9 years							
15-20 years							
1st stroke symptom duration >24 hours							
Presentation with hemiparesis							
Stroke risk factors							
Radiation arteriopathy							
Moyamoya							
Neurofibromatosis, type 1							
Cavernous malformation							
AVM							
Aneurysm							

§ any self-reported recurrent stroke, based on new (2009) questionnaire

RT=radiation therapy

*or median (IQR) if not normally distributed

HR=hazards ratio from univariate Cox proportional hazards models

Table 13. Independent predictors of recurrent stroke

Variables will depend on results of univariate analysis

Predictor	HR	95% CI	p-value
Sex			
Male			
Female			
Race			
White, non-Hispanic			
Black			
Hispanic			
Other			
Age at cancer diagnosis			
0-4.9 years			
5-9.9 years			
10-14.9 years			
15-20 years			
Cancer diagnosis			
Brain tumor			
Leukemia			
Hodgkin's			
Radiation Treatment			
No radiation therapy (RT)			
RT, any			
Any cranial RT			
Cranial RT dose>xx Gy			
Mantle RT			
Mantle RT dose >35 Gy			
Chemotherapy			
No chemotherapy			
Chemotx, alkylating agent			
Chemotx, methotrexate			
Chemotx, other			
Recurrent or secondary tumor			
Recurrent tumor (requiring tx)			
Secondary malignancy			
Age at RT, years, mean (SD)*			
Age at RT (categorical)			
0-4.9 years			
5-9.9 years			
10-14.9 years			
15-20 years			
Age at 1st stroke, years, mean (SD)*			
Age at 1st stroke (categorical)			
0-4.9 years			
5-9.9 years			
10-14.9 years			
15-19.9 years			
20-29.9 years			
30-39.9 years			
Interval from RT to 1st stroke, y, mean (SD)*			
Interval from RT to 1st stroke (categorical)			
0-4.9 years			
5-9.9 years			
10-14.9 years			
15-20 years			
1st stroke symptom duration >24 hours			

§ any self-reported recurrent stroke, based on new (2009) questionnaire

RT=radiation therapy

*or median (IQR) if not normally distributed

HR=hazards ratio from univariate Cox proportional hazards models

Appendix 4: List of Figures:

1. SA1
    a. Fig1. Cumulative incidence curve for stroke from 5 years after cancer diagnosis, stratified by cancer-type (brain tumor, Hodgkins, lymphoma).
    b. Fig 2. Cumulative incidence curve for stroke from 5 years after cancer diagnosis, stratified by prior radiation therapy.
    c. Note: Might consider three Cumulative incidence curves for stroke, one for each cancer-type, each stratified by radiation therapy
2. SA 3
    a. Fig 4. Cumulative incidence curve for recurrent stroke after first stroke, stratified by cancer-type (brain tumor, Hodgkins, lymphoma).
    b. Fig 5. Cumulative incidence curve for recurrent stroke after first stroke, stratified by prior radiation therapy.
    c. Note: Might consider three Cumulative incidence curves for recurrent stroke, one for each cancer-type, each stratified by radiation therapy