



## UvA-DARE (Digital Academic Repository)

### Radiation-associated adverse events after childhood cancer

van Dijk, I.W.E.M.

**Publication date**  
2014

[Link to publication](#)

#### **Citation for published version (APA):**

van Dijk, I. W. E. M. (2014). *Radiation-associated adverse events after childhood cancer*. [Thesis, fully internal, Universiteit van Amsterdam].

#### **General rights**

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

#### **Disclaimer/Complaints regulations**

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, P.O. Box 19185, 1000 GD Amsterdam, The Netherlands. You will be contacted as soon as possible.

# Chapter 6

## Radiation-associated cerebrovascular events in long-term childhood cancer survivors

Irma W.E.M. van Dijk<sup>1</sup>, Helena J.H. van der Pal<sup>2,3</sup>, Rob M. van Os<sup>1</sup>, Yvo B.W.E.M. Roos<sup>4</sup>, Elske Sieswerda<sup>2,3</sup>, Elivra C. van Dalen<sup>3</sup>, Cécile M. Ronckers<sup>3</sup>, Foppe Oldenburger<sup>1</sup>, Huib N. Caron<sup>2,3</sup>, Caro C.E. Koning<sup>1</sup>, Leontien C.M. Kremer<sup>2,3</sup>

<sup>1</sup>Department of Radiation Oncology, Academic Medical Center (AMC), Amsterdam, The Netherlands

<sup>2</sup>Department of Medical Oncology, AMC, Amsterdam, The Netherlands

<sup>3</sup>Department of Pediatric Oncology, Emma Children's Hospital / AMC, Amsterdam, The Netherlands

<sup>4</sup>Department of Neurology, AMC, Amsterdam, The Netherlands

*(Manuscript in preparation)*

## Abstract

### Purpose

To evaluate the incidence and severity of symptomatic cerebrovascular accidents (CVAs) and treatment-related risk factors in long-term childhood cancer survivors.

### Patients and Methods

The single-center study cohort comprised 1362 survivors treated for a wide range of diagnoses. Physical radiation doses for cranial and supradiaphragmatic radiation therapy (CRT, SDRT) were converted into the equivalent dose in 2-Gy fractions (EQD<sub>2</sub>) to assess dose-effect relationships. We used multivariable Cox regression analyses including sex, age at diagnosis, and treatment-related risk factors to evaluate risk factors.

### Results

At a median age of 31.2 years, 28 survivors had a first CVA. The median time from primary cancer diagnosis was 24.9 years. The 35-year cumulative incidence in the CRT only group was 13.1% (95%CI, 3.5-21.8%), and in the SDRT only group 6.3% (95%CI, 0-12.3%). For the group treated with both CRT and SDRT, the 35 year cumulative incidence was 22.6% (95%CI, 6.2-36.0%). The incidence rate for a first CVA was 108.2 per 100,000 person-years. The EQD<sub>2</sub> was available for 411 (93.8%) of the 438 survivors treated with CRT and/or SDRT. Our analyses showed that both treatment locations significantly increased the risk of CVA in a dose-dependent manner (HR<sub>CRT</sub> 1.02 Gy<sup>-1</sup>; 95%CI, 1.01-1.03, and HR<sub>SDRT</sub> 1.04 Gy<sup>-1</sup>; 95%CI, 1.02-1.05).

### Conclusion

Our study showed that survivors treated with CRT and/or SDRT have a very high risk of CVAs, as compared with survivors not exposed to these radiation locations. Continuing follow-up with special attention for preventive strategies to reduce the risk of CVAs is needed.

## Introduction

Owing to ongoing improving diagnostic and treatment techniques, childhood cancer survival rates have increased impressively over the last decades, resulting in a continuously growing population of long-term survivors.<sup>1,2</sup> At the same time, survivors are at risk of numerous tumor- and treatment-related late adverse events.<sup>3,4</sup> Cerebrovascular accidents (CVAs) including ischemia, infarction, and hemorrhage in the central nervous system (CNS) are among the most serious events, since they often have life-threatening or disabling consequences, or result in death.

Radiation-associated vascular disease is an adverse event that has been extensively described in several case reports, case series and cohort studies.<sup>5-8</sup> A number of cohort studies that evaluated stroke as late effect in childhood cancer survivors identified cranial radiation therapy (CRT) as main risk factor for stroke.<sup>9-13</sup> In pediatric Hodgkin's disease survivors, mantle field irradiation increased the risk of stroke.<sup>14</sup> A study on adults treated for head-and-neck cancer showed an increased risk of ischemic stroke after neck irradiation,<sup>15</sup> but cervical irradiation was not identified as a risk factor for stroke in childhood cancer survivors.<sup>12</sup> However, asymptomatic carotid artery disease, an early risk factor for stroke, appeared to be more prevalent in childhood cancer survivors treated with neck irradiation.<sup>16,17</sup>

The aim of this study was 1) to determine the cumulative incidence and the incidence rate of a first symptomatic CVA 5 years or more after primary cancer diagnosis, 2) to investigate potential risk factors, and 3) to assess dose-effect relationships for cranial and supradiaphragmatic radiation therapy using the equivalent dose in 2-Gy fractions (EQD<sub>2</sub>).

## Patients and Methods

### *Study cohort*

The original study cohort consisted of 1362 children, who were diagnosed and treated for a primary cancer at the age of 18 years and younger between January 1<sup>st</sup> 1966 and January 1<sup>st</sup> 1996 in the Emma Children's Hospital/Academic Medical Center (EKZ/AMC), Amsterdam, and who survived 5 years or more after diagnosis. Details on the methods of patient selection and data collection have been described earlier.<sup>3,18</sup>

### *Data collection and follow-up*

The EKZ/AMC Childhood Cancer Registry that was established in 1966, contains complete data on survivors' characteristics, cancer diagnosis and therapy, including treatment for recurrences and second tumors. For each patient, we collected data on surgery, chemotherapy and radiotherapy for the primary cancer, metastatic or recurrent disease and for subsequent tumors preceding the first CVA. Specific and detailed information on radiation schedules, fractionation and total dose were obtained from patient's individual treatment sheets.

Since 1996, all 5-year survivors are invited to the Outpatient Clinic for Late Effects of Childhood Cancer (Polikliniek Late Effecten Kindertumoren; PLEK) for the assessment and care of late tumor- and treatment-related adverse events. Information on follow-up and the prevalence of CVAs were retrieved from the PLEK database and clinical records. CVAs were defined and graded independently by two of the authors (HvdP, YR) using the Common Terminology Criteria for Adverse Events (CTCAEv3.0).<sup>19</sup> Discrepancies were solved by consensus, and when no consensus was reached, final resolution was achieved by a third author (LK). The end of follow-up date was defined as 1) date of first CVA, 2) date of death, 3) date of last follow-up.

#### *Outcome definition*

The outcome definition was first and recurrent CVAs occurring 5 years or more after primary cancer diagnosis, including symptomatic cerebrovascular ischemia and hemorrhage. The CTCAEv3.0 classifies symptomatic CVAs as CNS cerebrovascular ischemia Grade 3 as TIA ( $\leq 24$  hours), Grade 4 as a cerebral vascular accident (CVA, stroke) with neurologic deficit  $>24$  hours, and Grade 5 as an event-related death. Symptomatic CNS hemorrhage distinguishes Grade 2 through 5: Grade 2 indicates a medical intervention, whereas Grade 3 indicates ventriculostomy, ICP monitoring, intraventricular thrombolysis, or surgery. Grade 4 hemorrhagic events have life-threatening or disabling consequences, and Grade 5 is an event-related death. Ischemia Grade 2 and hemorrhage Grade 1 are asymptomatic, radiographic findings that were registered as non-cases.<sup>19</sup>

#### *Calculation of equivalent dose in 2-Gy fractions for radiotherapy*

We converted the physical doses delivered for all treatments preceding the outcome into the equivalent dose in 2-Gray fractions (EQD<sub>2</sub>). The EQD<sub>2</sub> for external beam radiation was calculated with the formula below, based on the linear-quadratic (LQ) model:

$$\text{EQD}_2 = D \cdot \frac{d + \alpha/\beta}{2 + \alpha/\beta} \quad [1]$$

The total dose  $D$  represents the number of fractions multiplied by the fractionation dose  $d$ . We used an  $\alpha/\beta$  ratio of 3 Gy for late responding vascular tissues.<sup>20,21</sup> The rationale and methodology of using the EQD<sub>2</sub> has been described previously (Van Dijk et al; submitted).

The current study also includes survivors treated with continuous low dose rate (LDR) brachytherapy. When treated with LDR brachytherapy, exposed tissues do not have a chance to repair completely. Consequently, to convert physical dose received by means of continuous LDR brachytherapy into the EQD<sub>2</sub>, formula [1] needs to be modified. The modified EQD<sub>2</sub> formula for continuous irradiation incorporates a factor  $g$  to allow for incomplete repair:

$$\text{EQD}_2 = D \cdot \frac{(d \cdot g + \alpha/\beta)}{2 + \alpha/\beta} \quad [2]$$

In case of a continuous single exposure, the fraction dose  $d$  equals  $D$ ;  $D$  is the total dose, i.e.

dose rate multiplied by exposure time. As in formula [1], we used an  $\alpha/\beta$  of 3 Gy. The incomplete repair factor  $g$  depends on the exposure time and the repair half time. The formula to calculate  $g$  is:

$$g = \frac{2 \cdot [\mu \cdot t - 1 + \exp(-\mu \cdot t)]}{(\mu \cdot t)^2} \quad [3]$$

in which  $t$  = exposure time;  $\mu$  has to be calculated as well:

$$\mu = \frac{\log_e 2}{T_{1/2}} \quad [4]$$

where  $T_{1/2}$  represents the half repair time, i.e. the time needed to repair half of the DNA damage caused by radiation.<sup>21</sup> For late responding tissue such as blood vessels, the  $T_{1/2}$  is estimated at 3.5 hours.<sup>22,23</sup>

### *Statistical analysis*

The outcome of interest was a first symptomatic CVA occurring at least 5 years after primary cancer diagnosis. Asymptomatic CVAs (i.e., ischemia Grade 2, and hemorrhage Grade 1) were defined as non-cases. Two survivors with symptomatic events that occurred within 5 years after primary cancer diagnosis were excluded from all analyses.

We estimated the cumulative incidence for a first CVA using survival analyses. The incidence rate for a first symptomatic CVA was calculated as the number of survivors with a CVA divided by the number of person-years at risk. Person-years at risk were computed starting 5 years from the date of primary cancer diagnosis to the date of the first CVA, death, or last follow-up.

In crude multivariable Cox regression analyses we investigated different radiation therapy locations, including head (brain and/or facial), neck, thorax, (mini)mantle field, spine, and total body, each in a separate models adjusted for sex, age at diagnosis, and the treatment-related risk factors brain surgery and chemotherapy. We then captured the aforementioned locations in two main treatment groups: cranial radiotherapy (CRT) and supradiaphragmatic radiotherapy (SDRT). CRT included irradiation of (a part of) the brain as a consequence of brain only, and/or as part of the combinations craniospinal irradiation (CSI), (mini)mantle field irradiation (including the occiput), and/or TBI. CRT also included anterior-posterior orbital radiation fields and orbital brachytherapy. SDRT included irradiation of the neck, and/or thorax, and/or (mini)mantle field, and/or spine (whether or not as part of CSI), and/or TBI. We also investigated the correlation between the locations CRT and SDRT by calculating Pearson's correlation coefficient.

In the first model, CRT and SDRT were evaluated dichotomously (yes/no), and in the second model we evaluated the association between radiation dose (EQD<sub>2</sub>) and symptomatic CVAs per treatment location. Assumptions for linearity were evaluated and were not violated.

All data were analyzed with SPSS version 21.0.1 (Statistical Package for the Social Sciences, Chicago, IL) for Windows, and the statistical program R, version 2.13.1 (<http://www.R-project.org>).

## Results

### Study cohort

Table 1 presents the characteristics of the childhood cancer survivors with and without a CVA. The median follow-up duration for the whole cohort was 23.8 (range, 5.0-45.3) years and the median attained age was 31.0 (range, 5.2-56.0) years. Of the 1360 survivors included in the analyses, 217 (16.0%) developed subsequent tumors. Radiotherapy was part of the treatment in 56 (25.9%) of these survivors, of whom 14 did not receive radiotherapy for their primary tumor. Of the 28 survivors with a CVA, one did not receive any radiotherapy, and 23 (82.1%) had CRT for the primary and/or subsequent tumor preceding the CVA.

<b>Table 1.</b> Characteristics of the EKZ/AMC childhood cancer survivor cohort (N = 1360*)		
Characteristic	Survivors with CVA N = 28 (%)	Survivors without CVA N = 1332 (%)
Sex		
Male	15 (53.6)	728 (54.7)
Female	13 (46.4)	604 (45.3)
Age at primary cancer diagnosis (years)		
Median (range)	6.2 (1.0-12.7)	6.0 (0-17.8)
0-5	10 (35.7)	585 (43.9)
>5-10	13 (46.4)	364 (27.3)
>10-15	5 (17.9)	304 (22.8)
>15	0	79 (5.9)
Primary cancer diagnosis		
Brain/Central nervous system	9 (32.1)	100 (7.5)
Leukemia	5 (17.9)	328 (24.6)
Lymphom <sup>a</sup>	10 (35.7)	249 (18.7)
Soft tissue sarcoma	3 (10.7)	148 (11.1)
Kidney/Wilms' tumor	1 (3.6)	188 (14.1)
Other <sup>t</sup>	0	319 (23.9)
Calendar year of primary cancer diagnosis		
1966-1975	8 (28.6)	204 (15.3)
1976-1985	17 (60.7)	527 (39.6)
1986-1995	3 (10.7)	601 (45.1)
Primary and subsequent cancer treatment <sup>‡</sup>		
Brain surgery		
Yes	10 (35.7)	115 (8.6)
No	18 (64.3)	1217 (91.4)
Chemotherapy		
Yes	20 (71.4)	1155 (86.7)
No	8 (28.6)	175 (13.1)
Unknown	0	2 (0.2)
Radiotherapy		
CRT	23 (82.1)	320 (24.0)
Brain	15 (53.6)	213 (16.0)

**Table 1.** Characteristics of the EKZ/AMC childhood cancer survivor cohort (N = 1360\*) (continued)

Brain as part of (mini)mantle field	1 (3.6)	18 (1.4)
Brain as part of CSI	7 (25.0)	77 (5.8)
Brain as part of TBI	1 (3.6)	31 (2.3)
SDRT	17 (60.7)	237 (17.8)
Neck (incl. mini mantle field)	3 (10.7)	48 (3.6)
Thorax (excl. mantle field)	5 (17.9)	67 (5.0)
Mantle field	1 (3.6)	15 (1.1)
Spine, ± CSI	7 (25.0)	85 (6.4)
TBI	1 (3.6)	31 (2.3)
Follow-up time since primary cancer diagnosis (years)		
Median (range)	24.9 (5.6-41.2)	23.8 (5.0-45.3)
5-15	3 (10.7)	149 (11.2)
>15-2 <sup>5</sup>	11 (39.3)	594 (44.6)
>25-35	13 (46.4)	445 (33.4)
>35	1 (3.6)	144 (10.8)
Attained age at end of follow-up time (years)		
Median (range)	31.2 (15.1-46.5)	31.0 (5.2-56.0)
5-15	0	53 (4.0)
>15-25	6 (21.4)	308 (23.1)
>25-3 <sup>5</sup>	11 (39.3)	521 (39.1)
>35-45	10 (35.7)	367 (27.6)
>45	1 (3.6)	83 (6.2)
Vital status at end of follow-up		
Alive	22 (78.6)	1178 (88.4)
Deceased	6 (21.4)	154 (11.6)

EKZ/AMC Emma Children's Hospital/Academic Medical Center, CVA cerebrovascular accident (symptomatic only as graded according to the CTCAEv.3.0), CSI craniospinal irradiation, TBI total body irradiation  
<sup>2</sup>2 survivors who had a CVA within 5 years after primary cancer diagnosis were excluded from the complete cohort (N=1362).

<sup>1</sup>Includes 116 bone tumors, 85 neuroblastoma, 21 retinoblastoma, 43 germ cell tumors, 13 thyroid carcinoma, 12 hepatoblastoma, 11 malignant histiocytosis, 18 miscellaneous.

<sup>3</sup>Brain surgery, chemotherapy and/or radiotherapy for the primary malignancy and/or subsequent tumors preceding the CVA.

### Radiotherapy

Table 2 shows detailed information on radiation location and dose for all treatments included. In total, 184 survivors had CRT without SDRT, 95 had SDRT without CRT, and 159 survivors received both CRT and SDRT. Calculation of Pearson's coefficient showed that the locations CRT and SDRT were weakly correlated ( $r^2 = -0.198$ ).

We retrieved detailed information about radiation schedules for 411 (93.8%) of the 438 survivors treated with CRT and/or SDRT. The high dose values and wide dose ranges are the result of dose summations for all treatments, including brachytherapy. The median doses for CRT dose and SDRT were higher among survivors with a CVA (39.2 Gy vs. 26.3 Gy, and 33.2 Gy vs. 24.2Gy, respectively).

**Table 2.** Radiation location and cumulative equivalent dose for CRT and/or SDRT (N = 438) in the EKZ/AMC childhood cancer survivor cohort

	Survivors with CVA, N = 28 (%)				Survivors without CVA, N = 410 (%)			
	Total, N	RT dose available, N	EQD <sub>2</sub> (Gy), median (range)	Total, N	RT dose available, N	EQD <sub>2</sub> (Gy), median (range)	Total, N	EQD <sub>2</sub> (Gy), median (range)
CRT*	23	22	39.2 (22.3-76.6)	320	300	26.3 (10.8-247.5)	320	26.3 (10.8-247.5)
Brain only	15	14	24.8 (22.3-76.6)	213	198	24.8 (10.8-247.5)	213	24.8 (10.8-247.5)
Brain as part of (Mini)Mantle field	2	1	28.3	18	17	29.1 (19.4-40.7)	18	29.1 (19.4-40.7)
Brain as part of CSI	7	7	51.1 (51.0-54.4)	77	76	48.6 (14.2-70.6)	77	48.6 (14.2-70.6)
Brain as part of TBI	1	1	21.6	31	31	15.8 (1.0-21.6)	31	15.8 (1.0-21.6)
SDRT*	17	16	33.2 (15.0-41.1)	237	231	24.8 (1.6-165.6)	237	24.8 (1.6-165.6)
Neck (incl.minimantle field)	3	2	38.6 (37.3-40.0)	48	45	38.7 (8.0-165.6)	48	38.7 (8.0-165.6)
Thorax (excl.mantle field)	5	5	25.0 (15.0-31.0)	67	67	24.0 (4.1-70.0)	67	24.0 (4.1-70.0)
Mantle field	1	1	40.0	15	15	30.8 (20.6-39.7)	15	30.8 (20.6-39.7)
Spine whether or not as part of CSI	7	7	34.6 (31.1-41.1)	85	84	29.5 (1.6-53.6)	85	29.5 (1.6-53.6)
TBI	1	1	21.6	31	31	15.8 (1.0-21.6)	31	15.8 (1.0-21.6)

CRT cranial radiation therapy, SDRT supradiaphragmatic radiation therapy, EKZ/AMC Emma Children's Hospital/Academic Medical Center, CVA, cerebrovascular accident (symptomatic only as graded according to CTCAEv.3.0),<sup>19</sup> CSI craniospinal irradiation, TBI total body irradiation

\*CRT and SDRT groups are not mutually exclusive.

**Table 3.** Characteristics of 28 survivors in the EKZ/AMC childhood cancer survivor cohort who had a (recurrent) CVA  $\geq 5$  years after primary cancer diagnosis

Id.	Sex	Cancer diagnosis	Age at cancer diagnosis (years)	Radiation field	Radiation dose (EQD <sub>2</sub> ; Gy)	CVA* (short name)	Grade*	Age at CVA (years)	Vital status at end of follow-up
1.	F	Brain/CNS	5.3	Cranial	Unknown	CNS ischemia	4	46.5	Alive
2.	M	Brain/CNS	5.8	Cranial / Spinal	52.1 / 34.1	CNS ischemia	4	36.0	Alive
3.	F	Brain/CNS	7.1	Cranial / Spinal	51.0 / 31.1	CNS hemorrhage	3	24.7	Alive
4.	M	Brain/CNS	7.7	Cranial / Spinal	54.4 / 37.7	CNS ischemia	4	30.2	Alive
5.	M	Brain/CNS Meningioma	8.2 23.1	Cranial / Spinal No RT	51.1 / 41.1 NA	CNS hemorrhage	2	26.1	Alive
6.	M	Brain/CNS	9.6	Cranial / Spinal	51.0 / 37.0	CNS ischemia	4	33.0	Dead
7.	F	Brain/CNS	10.1	Cranial / Spinal	53.8 / 34.6	CNS ischemia CNS ischemia CNS ischemia	4 4 4	36.3 40.0 41.6	Alive

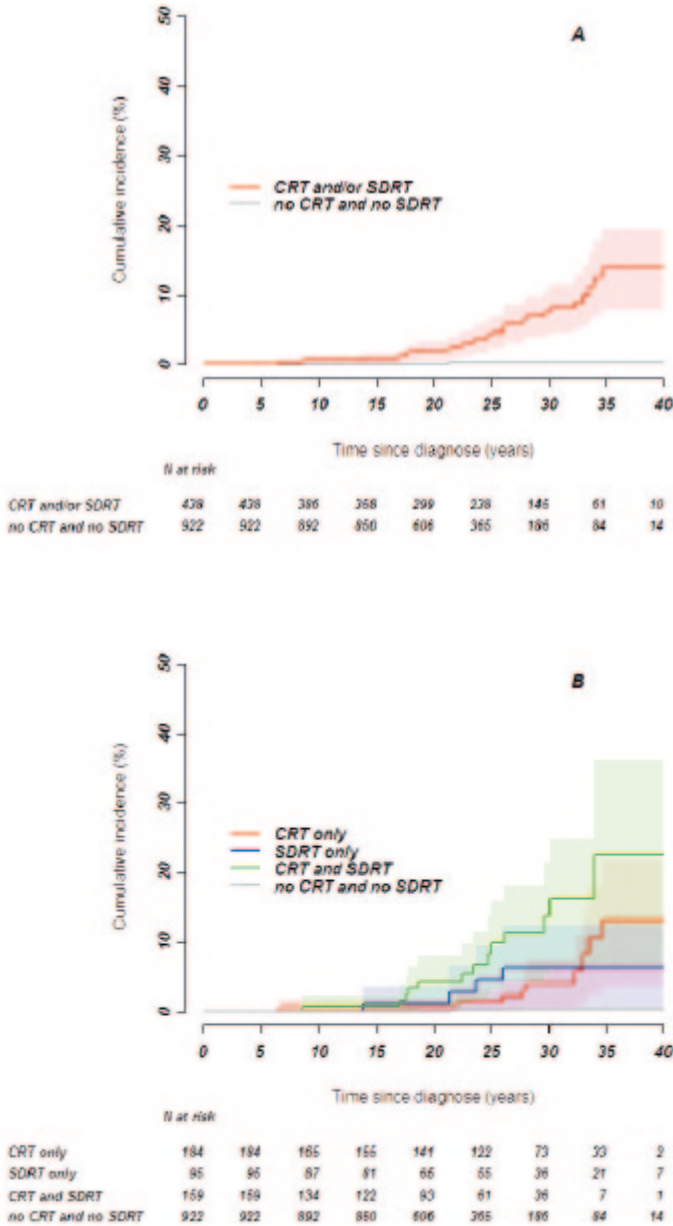
**Table 3.** Characteristics of 28 survivors in the EKZ/AMC childhood cancer survivor cohort who had a (recurrent) CVA  $\geq 5$  years after primary cancer diagnosis (continued)

Id.	Sex	Cancer diagnosis	Age at cancer diagnosis (years)	Radiation field	Radiation dose (EQD <sub>2</sub> ; Gy)	CVA* (short name)	Grade*	Age at CVA (years)	Vital status at end of follow-up
8.	M	Brain/CNS	10.1	Cranial	51.4	CNS ischemia	3	16.7	Alive
9.	F	Brain/CNS	11.3	Cranial / Spinal	51.0 / 32.4	CNS ischemia	3	22.0	Alive
10.	M	Leukemia	3.30	Cranial	24.8	CNS hemorrhage	5	28.3	Dead
11.	M	Leukemia Meningioma	3.5 26.2	Cranial / Chest Cranial	24.8 / 15.0 51.8	CNS hemorrhage	2	35.6	Alive
12.	M	Leukemia Meningioma	3.6 31.0	Cranial No RT	24.8 NA	CNS ischemia	4	37.1	Alive
13.	M	Leukemia	3.6	Cranial	24.8	CNS hemorrhage	2	31.4	Alive
14.	F	Leukemia	5.4	Cranial	24.8	CNS hemorrhage	4	38.4	Alive
15.	F	Leukemia	8.1	Cranial	24.8	CNS hemorrhage	3	30.1	Alive
16.	F	Lymphoma	2.6	Cranial / Chest	22.3 / 24.8	CNS ischemia	4	27.7	Alive
17.	M	Lymphoma	4.9	Cranial	24.0	CNS ischemia	4	31.0	Dead
18.	M	Lymphoma	4.9	Chest	40.0	CNS ischemia	3	31.0	Alive
19.	F	Lymphoma	6.6	Cranial / Chest	24.8 / 25.0	CNS ischemia	4	36.3	Alive
20.	F	Lymphoma	6.9	Cranial	24.5	CNS ischemia	3	41.6	Alive
21.	M	Lymphoma	7.0	Cranial / Neck	28.3 / 37.3	CNS hemorrhage	5	15.6	Dead
22.	F	Lymphoma	7.3	Neck	Unknown	CNS hemorrhage	3	28.7	Alive
23.	M	Lymphoma	11.8	Neck	40.0	CNS ischemia	4	35.4	Alive
24.	F	Lymphoma	12.7	Cranial / Chest	24.8 / 31.0	CNS hemorrhage	3	37.5	Alive
25.	M	Soft tissue sarcoma	1.0	No RT	NA	CNS ischemia	3	22.4	Dead
26.	M	Soft tissue sarcoma Leukemia Malignant histiocytoma	4.0 18.9 21.3	No RT TBI Cranial	NA 21.6 36.0	CNS ischemia	3	22.7	Dead
27.	F	Soft tissue sarcoma	5.4	Cranial	50.0	CNS ischemia	4	33.5	Alive
28.	F	Wilms' tumor	1.2	Chest	25.5	CNS ischemia	4	15.1	Alive

EKZ/AMC Emma Children's Hospital/Academic Medical Center, CVA cerebrovascular event, Id patient identification, EQD2 equivalent dose in 2-Gy fractions, F female, M male CNS centra, nervous system, RT radiotherapy, TBI total body irradiation, NA non-applicable

\*Defined and graded according to the CTCAEv.3.0.19

Table includes primary cancer diagnosis, and subsequent tumors preceding the first CVA with the exception of basal cell carcinomas.



**Figure 1.** Cumulative incidence and 95%CI of CVAs in the EKZ/AMC childhood cancer survivor cohort, for survivors treated with (A) CRT and/or SDRT, and for survivors in the separate treatment groups (B) CRT only, SDRT only, and CRT and SDRT combined, as compared with survivors who had neither CRT nor SDRT.

CI confidence interval, CVA cerebrovascular accident (symptomatic only as graded according the CTCAEv.3.0)<sup>19</sup>, EKZ/AMC Emma Children’s Hospital/Academic Medical Center, CRT cranial radiation therapy, SDRT supradiaphragmatic radiation therapy

*Incidence and severity of symptomatic CVA*

After a median follow-up of 24.9 years (range 5.6 – 41.2 years), and at a median age of 31.2 years (range 15.1 – 46.5 years), 28 survivors experienced a first symptomatic CVA (Table 3). The 35-year cumulative incidence for survivors treated with CRT only, SDRT only, or CRT and SDRT combined was 13.8% (95%CI, 7.7-19.4%) (Fig.1A). The 35-year cumulative incidence in the CRT only group was 13.1% (95%CI, 3.5-21.8%), and in the SDRT only group 6.3% (95%CI, 0-12.3%). For the group treated with both CRT and SDRT, the 35 year cumulative incidence was 22.6% (95%CI, 6.2-36.0%) (Figure 1B). The incidence rate was 108.2 per 100,000 person-years (95%CI, 74.6-156.7 per 100,000 person-years).

Eighteen survivors had ischemic events Grade 3 or 4, and 10 had hemorrhagic Grade 2 through 5 CVAs. Two patients had one or more recurrent CVAs, of whom one a recurrent Grade 3 CVA (i.e., TIA) shortly after discontinuation of prophylactic anticoagulation. Six of the hemorrhagic CVAs occurred from cavernous malformations, of which one was located in the thoracic spine (Id.3).

Twenty-two (78.6%) of the 28 survivors with CVAs received any form of CRT for their primary malignancy, and one had CRT for subsequent tumors, without being irradiated for the first malignancy (Id.26). Two survivors received chest irradiation without CRT, one of whom was diagnosed with heart failure (Id.18), and the other with cardiomyopathy and stenosis of the internal carotid artery (Id.28). Two other survivors were treated with neck irradiation only (Id.22, 23). One survivor had no radiotherapy at all (Id.25). At the end of follow-up, six survivors had died. Two due to their hemorrhagic CVA, one due to second tumor complications, and two because of other reasons. One survivor without any radiotherapy died of cardiomyopathy (Id.25).

*Treatment-related risk factors for symptomatic CVA*

The first crude multivariable models including sex, age at diagnosis, and the treatment-related risk factors brain surgery and chemotherapy, showed that radiotherapy to the head significantly increased the risk of CVA (HR 10.65; 95%CI, 3.81-29.77). Investigation of brain and facial RT separately showed that brain RT was a significant risk factor for developing a CVA (HR 10.24; 95%CI, 3.66-28.65), whereas facial RT was not (HR 2.46; 95%CI, 0.32-18.84). Radiation of the thorax and the neck did not significantly increase the risk of CVA (HR 2.67; 95%CI, 0.97-7.37, and HR 3.40; 95%CI, 0.96-12.09, respectively), nor did mantle field irradiation and TBI (HR 3.78; 95%CI, 0.47-30.63, and HR 5.32; 95%CI, 0.69-40.80, respectively). Spinal RT did significantly increase the risk of CVA (HR 3.16; 95%CI, 1.03-9.73), but adding brain RT to this model showed that brain RT was the only significant risk factor (HR 9.65, 95%CI 3.42-27.23) whereas spinal RT was not. Craniospinal irradiation (CSI) significantly increased the risk of CVA (HR 3.37; 95%CI, 1.06-10.70).

We then classified the different treatment locations into two main groups, i.e. CRT ((part of the) brain only, or as part of CSI and/or TBI), and SDRT (RT of the neck, thorax, (mini) mantle, and/or spine). In Table 4, the results of the multivariable Cox regression models

are presented. The first model shows that CRT and SDRT were the only determinants that significantly increased the risk of a symptomatic CVA ( $HR_{CRT}$  8.74; 95%CI, 3.04-25.11, and  $HR_{SDRT}$  4.19; 95%CI, 1.84-9.57). The second model shows significant independent dose-effect associations for both locations ( $HR_{CRT}$  1.02 Gy<sup>-1</sup>; 95%CI, 1.01-1.03, and  $HR_{SDRT}$  1.04 Gy<sup>-1</sup>; 95%CI, 1.02-1.05, respectively). None of the other variables included was significant in any of the two models.

**Table 4.** Multivariable Cox regression models\* for a first symptomatic CVA in the EKZ/AMC childhood cancer survivor cohort

Model 1	HR	(95%CI)
Sex (F/M)	0.87	(0.40-1.87)
Age at diagnosis (years)	0.93	(0.84-1.03)
Brain surgery (yes/no)	1.33	(0.56-3.12)
Chemotherapy (yes/no)	0.51	(0.21-1.23)
CRT† (yes/no)	8.74	(3.04-25.1)
SDRT† (yes/no)	4.19	(1.84-9.57)
<i>Model 2</i>		
Sex (F/M)	0.82	(0.37-1.81)
Age at diagnosis (years)	0.94	(0.85-1.04)
Brain surgery (yes/no)	2.04	(0.81-5.11)
Chemotherapy (yes/no)	0.75	(0.29-1.91)
CRT† (EQD <sub>2</sub> per Gy)	1.02	(1.01-1.03)
SDRT† (EQD <sub>2</sub> per Gy)	1.04	(1.02-1.05)

CVA cerebrovascular accident, EKZ/AMC Emma Children's Hospital/Academic Medical Center, HR hazard ratio, CI confidence interval, F female, M male, CRT cranial radiation therapy (i.e., (a part of) brain only, and/or brain as part from (mini)mantle field (including the occiput), and /or craniospinal irradiation, and/or total body irradiation), SDRT supradiaphragmatic radiation therapy (i.e. irradiation of the neck, thorax, (mini)mantle, spine, and total body)

\*Two survivors with a symptomatic CVA <5 years after primary cancer diagnosis were excluded from the cohort and the analyses.

†Treatment groups are not mutually exclusive.

## Discussion

In our cohort of long-term childhood cancer survivors, we identified 28 survivors who experienced a first symptomatic CVA after a median follow-up time of 24.9, and at a median age of 31.2 years. Our study demonstrated CRT and SDRT to increase the risk of CVAs, and we assessed significant dose-effect relationships for these two treatment locations and the occurrence of CVAs. The incidence rate of 108.2 per 100,000 person-years was remarkably higher as compared to crude rates ranging from 5.8 to 39.8 per 100,000 person-years that have been reported among young adults in the general population.<sup>24</sup>

Other studies that have evaluated stroke in childhood cancer survivors are summarized in Table 5. They focused on specific diagnoses,<sup>9,10,14</sup> or radiation treatment locations,<sup>11,13</sup> whereas we evaluated CVAs in childhood cancer survivors treated for a wide range of pri-

mary cancer diagnoses, including more than one treatment location. In agreement with other studies,<sup>9-13</sup> we demonstrated that the risk of CVAs increased with higher CRT dose. Bowers *et al* showed a CRT dose-dependent association for the risk of late-occurring stroke by using dose categories,<sup>9</sup> whereas we used EQD<sub>2</sub> values on a continuous scale. In contrast to our study, in which we did not include radiation volumes, Campen *et al* used information from medical records to categorize CRT fields in order to estimate the prescribed radiation dose to the circle of Willis. They showed that higher doses to the circle of Willis increased the risk of stroke.<sup>10</sup> In another study that evaluated long-term cerebrovascular mortality, absorbed doses to specific anatomical sites in the brain were estimated in childhood cancer patients treated with any radiotherapy. The authors concluded that higher radiation dose to the brain significantly increased the risk of cerebrovascular mortality.<sup>11</sup> Two studies by Mueller *et al.* also confirmed a CRT dose-dependent relationship for stroke risk.<sup>12,13</sup> One of these studies investigated the risk of stroke after cranial and neck RT, and showed that none of the patients with neck RT alone had a stroke. In contrast, we identified two survivors with neck RT alone having a CVA, however, these events were too few to demonstrate a significant increased risk of CVA after neck RT.

The only study that evaluated supradiaphragmatic RT was a study including pediatric Hodgkin's disease survivors. In that study, mantle field irradiation was associated with an increased risk of stroke,<sup>14</sup> in contrast with our crude models in which we analyzed different treatment locations separately. In our cohort we could not demonstrate significantly increased risks of CVAs after (mini)mantle field RT, nor after thoracic RT and TBI. Spinal RT, however, did increase the risk of CVAs, but when we added CRT to the model with spinal RT, CRT was the only significant risk factor.

Because of the complexity of different combinations of radiation locations per survivor, we captured the locations in the two treatment groups CRT and SDRT. Dichotomously, CRT was the strongest predictor as compared with SDRT (model 1), however, the HR<sub>SDRT</sub> per Gy EQD<sub>2</sub>, expressing the dose-effect relationship, was slightly higher than the HR<sub>CRT</sub> per Gy EQD<sub>2</sub> (model 2). One of the explanations for this seemingly reversal of the association includes the relatively larger dose range for CRT as compared with SDRT. Additionally, the greater number of missing dose values might partly have influenced this effect, however, when we repeated the analyses excluding the cases with brachytherapy or the ones with missing dose values, results were similar. Nevertheless, our results reflect the interest of using continuous dose values when evaluating radiation-associated effects, especially when more than one treatment location is involved.

Six of the 10 hemorrhagic CVAs occurred from cavernous malformations. Furthermore, our data showed that survivors who experienced a first ischemic CVA and who used anticoagulants, did not have recurrent events. One patient developed a TIA shortly after discontinuation of the anticoagulant; it is not clear, though, whether a causal relationship exists.

Strengths of our study include the nearly complete treatment data for the primary malignancy and subsequent tumors. To our knowledge, we are the first to include treatment

data for subsequent tumors, and we succeeded in collecting detailed information about radiation schedules for almost 94% of the survivors treated with CRT and/or SDRT. We converted physical prescribed dose into the EQD<sub>2</sub> to assess the relationship between the doses for two treatment locations and the occurrence of CVAs. Doing so allowed us to summate radiation doses delivered by different treatment modalities, such as external beam radiation and brachytherapy. Another strength is the standardized definition and grading according to the CTCAEv.3.0.<sup>19</sup>

An important limitation of our study is the unavailability of a healthy control population, which restricted us to comparisons with non-exposed cancer survivors within the cohort, i.e., the survivors not treated with CRT and/or SDRT. However, we calculated the incidence rate for CVAs, which we compared to population-based reference values. Another limitation is the lack of information about patient-related risk factors for CVAs, such as hypertension, smoking and obesity. Furthermore, we must realize that the EQD<sub>2</sub> represents the prescribed dose, which is not the same as the actually absorbed dose in organs at risk. It would be preferable to combine EQD<sub>2</sub> calculations with dose reconstruction methods.<sup>11</sup> In addition, we did not consider the time between treatments when adding up the doses for the primary malignancy, recurrences, and/or subsequent tumors. Nevertheless, using the EQD<sub>2</sub> enabled a uniform comparison of different radiation schedules and treatment modalities, which is not possible when the prescribed dose is used.

In summary, our study showed both CRT and SDRT to increase the risk of CVAs in childhood cancer survivors, as compared with survivors not exposed to these radiation locations. Larger cohort studies are warranted to investigate the risk of exposed survivors in combination with patient-related risk factors such as smoking, hypertension and obesity. Furthermore, continuing follow-up and additional research with special attention for preventive strategies to reduce the risk of CVAs is needed.

**Table 5.** Overview of childhood cancer survivor cohort studies evaluating the risk of stroke and cerebrovascular mortality

Study topic and publication	Stroke				Mortality	
	Risk of first and recurrent stroke	Radiation, atherosclerotic risk factors, and stroke risk	Cranial irradiation and stroke risk	Late-occurring stroke in leukemia and brain tumor survivors		Stroke as late treatment effect of HD
Study design	Mueller et al. <i>IJOBP</i> , 2013 <sup>12</sup> Single-center retrospective cohort study	Mueller et al. <i>IJOBP</i> , 2013 <sup>13</sup> Multi-institutional retrospective cohort study	Campen et al. <i>Stroke</i> , 2012 <sup>10</sup> Single-center retrospective cohort study	Bowers et al. <i>JCO</i> , 2006 <sup>9</sup> Multi-institutional retrospective cohort study (CCSS)	Bowers et al. <i>JCO</i> , 2005 <sup>14</sup> Multi-institutional retrospective cohort study (CCSS)	Haddy et al. <i>Brain</i> , 2011 <sup>11</sup> Multicenter retrospective cohort study
Study population	383 childhood cancer survivors 325 analyzed	14,358 childhood cancer survivors including 1876 CNS tumor survivors, compared with 4023 siblings	431 pediatric brain tumor survivors 265 had cranial RT	4828 Leukemia survivors; 1871 Brain tumor survivors 3846 Sibling controls	1926 HD survivors 3846 Sibling controls	4227 childhood cancer survivors
Period of childhood cancer diagnosis	1980 – 2009	1970 - 1986	1993 – 2002	1970 – 1986	1970 – 1986	<1985
Age at diagnosis	≤18 years	<21 years	<22 years; median 6, mean 6.5 (range 0-14) years	< 21 years; Leukemia survivors, mean 5.9 years (SD 4.5 years); Brain tumor survivors, mean 7.7 years (SD 5.2 years)	< 21 years; mean 13.8 years (SD 4.3 years)	<15 years
Survival since primary diagnosis	≥ 1 year from radiation therapy	>5 years	Not mentioned	≥5 years	≥5 years	≥5 years
Radiation therapy	Cranial and cervical radiation therapy	Direct brain RT categorized in 4 segments Indirect RT included head/neck RT	Whole brain, whole brain plus focal boost, or focal brain	Cranial radiation therapy; RT dose categories to Circle of Willis	Radiotherapy neck, chest, abdomen, pelvis	Any RT; dose estimations to anatomical points in the brain
Follow-up duration	Median 7.3 years (IQR 2.4-15.0 years)	Mean 23.3 years	Median 6.3 years	Leukemia survivors mean 17.9 years (SD 5.7 years) Brain tumor survivors mean 17.6 years (SD 5.8 years)	Mean 19.5 years (SD 5.9 years)	Mean and median 29 years (range 5-65 years)
Outcome	First and recurrent ischemic and hemorrhagic stroke	First late-occurring stroke (≥5 years after diagnosis)	Neurovascular events as late complication	Late-occurring stroke among childhood survivors of leukemia and brain tumor	Stroke as late treatment effect of childhood HD	Long-term cerebrovascular mortality

**Table 5.** Overview of childhood cancer survivor cohort studies evaluating the risk of stroke and cerebrovascular mortality (*continued*)

Outcome definition	Stroke			Mortality
	Stroke defined as physician diagnosis and symptoms consistent with stroke	Stroke defined as the earliest report of (self-reported) stroke in a time-to-event analysis	Physician-diagnosed stroke defined as an acute neurological syndrome with deficits conforming to a vascular territory, or TIA	
Time to event	Stroke defined as physician diagnosis and symptoms consistent with stroke Median time after CRT 12 years (IQR 5-18 years)	Stroke defined as the earliest report of (self-reported) stroke in a time-to-event analysis Mean time from diagnosis 18.6 years (range 5.2-38.1 years); in CNS tumor survivors 18.6 years (IQR 5.2-36.8 years)	Physician-diagnosed stroke defined as an acute neurological syndrome with deficits conforming to a vascular territory, or TIA Median 4.9 years (range 32 days-12.9 years)	Long-term cerebrovascular mortality Median 29 years, mean 27.9 years (range 8-46) years
Age at event	Stroke defined as physician diagnosis and symptoms consistent with stroke Median 24 years (IQR 17-33 years) for 1 <sup>st</sup> stroke Median 27 years (IQR 26-34 years) for recurrent stroke	Stroke defined as the earliest report of (self-reported) stroke in a time-to-event analysis Median 28.5 years (IQR 19-36 years); in CNS tumor survivors 27 years (IQR 19-35 years)	Physician-diagnosed stroke defined as an acute neurological syndrome with deficits conforming to a vascular territory, or TIA Median 7.6 (SD 5.3) years	Long-term cerebrovascular mortality Median 36 years, mean 34 years (range 11-57 years)
Methods	Chart review and phone interviews Imaging review in case of reported stroke	Questionnaires Radiation records of 98% of the 8510 participants known to have RT CRT assessment for 4 segments of the brain	Medical records Brain MRI reports Re-review of MRI images of survivors with stroke symptoms	Long-term cerebrovascular mortality Medical and radiological records, 'flagging', death certificates
Risk factors included in analyses	CRT and cervical radiation dose, age at radiation, sex	Race, sex, age at diagnosis, year of diagnosis, recurrence, chemotherapy, CRT dose categories, neck RT (yes/no), stroke risk factors (including hypertension, history of smoking, diabetes mellitus, history of neurofibromatosis, oral contraception pills).	Medical record abstraction Questionnaires Age at study, sex, race, chemotherapy, smoking, splenectomy, hypertension, diabetes mellitus, oral contraceptives	Long-term cerebrovascular mortality Age at diagnosis, treatment period, sex, follow-up interval after diagnosis, chemotherapy, including alkylating agents, vinca alkaloids, anthracyclines, antimetabolites and RT dose to the preopontine cistern

**Table 5.** Overview of childhood cancer survivor cohort studies evaluating the risk of stroke and cerebrovascular mortality (continued)

Findings	Stroke	Leukemia survivors:	Mortality
- 19 first strokes after CRT and 6 recurrent strokes	- 292 strokes, of which 125 (43%) in CNS tumor survivors;	- 37 strokes	- 23 deaths due to cerebrovascular diseases, including 12 cerebral hemorrhages, 6 cerebral infarctions, 5 unspecified strokes
- Overall rate of first stroke: 625 (95%CI 378-977) per 100,000 PY	- Stroke predictors in complete cohort: HR (50+ Gy vs no CRT) = 11.0 (95%CI 7.4-16.5),	- Stroke rate 58.6/100,000 PY (95%CI, 41.2-78.7),	- 24 strokes ≥5 years after diagnosis
- Cumulative incidence of first stroke: 2% (95%CI 0.01-5.3%) at 5 years;	- HR (30-49 Gy vs no CRT) = 5.9 (95%CI 3.5-9.9),	- RR (survivors vs siblings) = 6.4 (95%CI 3.0-13.8)	- 2 strokes <5 years after diagnosis
- 4% (95% CI 2.0-8.4%) at 10 years	- HR (1.5-29 Gy vs no CRT) = 1.8 (95%CI, 1.2-2.8),	- RR (CRT vs siblings) = 5.9 (95%CI 2.6-13.4),	- Stroke rate 83.6/100,000 PY (95%CI, 54.5-121.7)
- HR-CRT = 1.05 per Gy (95%CI 1.01-1.09)	- Stroke predictors for CNS tumor survivors: HR (50+ Gy vs no CRT) = 2.8 (95%CI 1.5-5.3),	- RR (no CRT vs siblings) = 4.0 (95%CI 1.4-11.5)	- RR (HD survivors vs controls) = 4.32 (95%CI 2.01-9.29)
- HR-males = 3.4 (95%CI, 1.1-10.3)	- HR (1.5-29 Gy vs no CRT) = 1.7 (95%CI 0.7-3.8),	- Brain tumor survivors: 63 strokes	- Stroke rate for mantle RT 109.8/100,000 PY (95%CI 70.8-161.0),
- HR-age at CRT = 1.12 (95%CI, 1.0-1.2, p=.01)		- Final model: RT to COW HR = 4.35 (95%CI, 0.97-19.6) and chemotherapy HR = 3.38 (95%CI, 9.2-12.5)	- Adjusted RRs (RT dose vs no RT):
			- RR (<10 Gy) 1.5 (95% CI 0.4-6.1)
			- RR (10 <30 Gy) 3.7 (95% CI 0.8-16.9)
			- RR (30 <50 Gy) 11.4 (95% CI 3.0-42.3)
			- RR (>50 Gy) 17.8 (95% CI 4.4-73)

HD Hodgkin's Disease, CCSS Childhood Cancer Survivor Study, CNS central nervous system, RT radiation therapy, SD standard deviation, IQR interquartile range, TIA transient ischemic accident, CRT cranial radiation therapy, MRI magnetic resonance imaging, CI confidence interval, HR hazard ratio Gy Gray, PY person years, RR relative risk

## References

1. Gatta G, Zigon G, Capocaccia R, *et al.* Survival of European children and young adults with cancer diagnosed 1995-2002. *Eur J Cancer* 2009; 45(6):992-1005.
2. Magnani C, Pastore G, Coebergh JW, *et al.* Trends in survival after childhood cancer in Europe, 1978-1997: report from the Automated Childhood Cancer Information System project (ACCIS). *Eur J Cancer* 2006; 42(13):1981-2005.
3. Geenen MM, Cardous-Ubbink MC, Kremer LC, *et al.* Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. *JAMA* 2007; 297(24):2705-2715.
4. Oeffinger KC, Mertens AC, Sklar CA, *et al.* Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med* 2006; 355(15):1572-1582.
5. Keene DL, Johnston DL, Grimard L, *et al.* Vascular complications of cranial radiation. *Childs Nerv Syst* 2006; 22(6):547-555.
6. Mitchell WG, Fishman LS, Miller JH, *et al.* Stroke as a late sequela of cranial irradiation for childhood brain tumors. *J Child Neurol* 1991; 6(2):128-133.
7. Humpl T, Bruhl K, Bohl J, *et al.* Cerebral haemorrhage in long-term survivors of childhood acute lymphoblastic leukaemia. *Eur J Pediatr* 1997; 156(5):367-370.
8. Jain R, Robertson PL, Gandhi D, *et al.* Radiation-induced cavernomas of the brain. *AJNR Am J Neuroradiol* 2005; 26(5):1158-1162.
9. Bowers DC, Liu Y, Leisenring W, *et al.* Late-occurring stroke among long-term survivors of childhood leukemia and brain tumors: a report from the Childhood Cancer Survivor Study. *J Clin Oncol* 2006; 24(33):5277-5282.
10. Campen CJ, Kranick SM, Kasner SE, *et al.* Cranial irradiation increases risk of stroke in pediatric brain tumor survivors. *Stroke* 2012; 43(11):3035-3040.
11. Haddy N, Mousannif A, Tukenova M, *et al.* Relationship between the brain radiation dose for the treatment of childhood cancer and the risk of long-term cerebrovascular mortality. *Brain* 2011; 134(Pt 5):1362-1372.
12. Mueller S, Sear K, Hills NK, *et al.* Risk of first and recurrent stroke in childhood cancer survivors treated with cranial and cervical radiation therapy. *Int J Radiat Oncol Biol Phys* 2013; 86(4):643-648.
13. Mueller S, Fullerton HJ, Stratton K, *et al.* Radiation, atherosclerotic risk factors, and stroke risk in survivors of pediatric cancer: a report from the Childhood Cancer Survivor Study. *Int J Radiat Oncol Biol Phys* 2013; 86(4):649-655.
14. Bowers DC, McNeil DE, Liu Y, *et al.* Stroke as a late treatment effect of Hodgkin's Disease: a report from the Childhood Cancer Survivor Study. *J Clin Oncol* 2005; 23(27):6508-6515.
15. Dorresteijn LD, Kappelle AC, Boogerd W, *et al.* Increased risk of ischemic stroke after radiotherapy on the neck in patients younger than 60 years. *J Clin Oncol* 2002; 20(1):282-288.
16. King LJ, Hasnain SN, Webb JA, *et al.* Asymptomatic carotid arterial disease in young patients following neck radiation therapy for Hodgkin lymphoma. *Radiology* 1999; 213(1):167-172.
17. Meeske KA, Siegel SE, Gilsanz V, *et al.* Premature carotid artery disease in pediatric cancer survivors treated with neck irradiation. *Pediatr Blood Cancer* 2009; 53(4):615-621.
18. Sieswerda E, Mulder RL, van Dijk IW, *et al.* The EKZ/AMC childhood cancer survivor cohort: methodology, clinical characteristics, and data availability. *J Cancer Surviv* 2013; 7(3):439-454.
19. Common Terminology Criteria for Adverse Events, version 3.0 (CTCAEv3.0). [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/ctcae3.pdf](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf). 2006.
20. Bentzen SM, Dorr W, Gahbauer R, *et al.* Bioeffect modeling and equieffective dose concepts in radiation oncology—terminology, quantities and units. *Radiother Oncol* 2012; 105(2):266-268.
21. Joiner MC, Bentzen SM. Fractionation: the linear-quadratic approach. In: Joiner MC, van der Kogel A, editors. *Basic Clinical Radiobiology*. London: Hodder Arnold, 2009: 102-119.
22. Bentzen SM, Saunders MI, Dische S. Repair halftimes estimated from observations of treatment-related morbidity after CHART or conventional radiotherapy in head and neck cancer. *Radiother Oncol* 1999; 53(3):219-226.
23. Turesson I, Thames HD. Repair capacity and kinetics of human skin during fractionated radiotherapy: erythema, desquamation, and telangiectasia after 3 and 5 year's follow-up. *Radiother Oncol* 1989; 15(2):169-188.
24. Marini C, Russo T, Felzani G. Incidence of stroke in young adults: a review. *Stroke Res Treat* 2010; 2011:535672.