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Neurocognitive function and health-related quality of life in a nationwide cohort of long-term childhood brain tumor survivors

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Abstract

Background. Childhood brain tumor survivors are at high risk of late effects, especially neurocognitive impairment. Limited data are available examining neurocognitive function and associations with quality of life (QoL) in childhood brain tumor survivors. Our aim was to examine neurocognitive function in childhood brain tumor survivors, and associations with QoL and symptom burden.

Methods. Five–year survivors of brain tumors over the age of 15 were identified in the Danish Childhood Cancer Registry ($n = 423$). Eligible and consenting participants completed neuropsychological tests and questionnaires assessing QoL, insomnia, fatigue, anxiety, and depression. Survivors treated with radiation ($n = 59$) were statistically compared with survivors not treated with radiation ($n = 102$).

Results. In total, 170 survivors participated (40.2% participation rate). Sixty-six percent of the survivors who completed neurocognitive tests ($n = 161$) exhibited overall neurocognitive impairment. Survivors treated with radiation, especially whole-brain irradiation, exhibited poorer neurocognitive outcomes than survivors not treated with radiation. Neurocognitive outcomes for survivors treated with surgery were below normative expectations. Furthermore, a number of survivors experienced significant fatigue (40%), anxiety (23%), insomnia (13%), and/or depression (6%). Survivors treated with radiation reported lower quality of life (QoL) and higher symptom burden scores than survivors not treated with radiation; particularly in physical functioning, and social functioning with symptoms of fatigue. Neurocognitive impairment was not associated with QoL or symptom burden.

Conclusions. In this study, a majority of the childhood brain tumor survivors experienced neurocognitive impairment, reduced QoL, and high symptom burden. Although not associated with each other, it is apparent that childhood brain tumor survivors experience not only neurocognitive dysfunction but may also experience QoL impairments and significant symptom burden.

Keywords

childhood brain tumor survivors | health-related quality of life | neurocognition | symptom burden

Primary brain tumors are the second most common childhood malignancy representing around 20% of all childhood malignancies.[1] Significant advance in the diagnosis and treatment of childhood brain tumors have led to an improved five–year survival rate now exceeding 75%.[2] Survivors of childhood cancer are at risk of late effects, and the cumulative incidence of a chronic health condition 30 years after diagnosis has been reported to be 73%.[3] Moreover, survivors of a brain tumor are more vulnerable to late effects compared to survivors of other childhood cancers.[4,5] Furthermore, a high burden of adverse events has been observed in 55% of childhood cancer survivors treated with radiation.[6] Treatment is often multimodal (surgery, chemotherapy, and/or radiation) with approximately 30% of children receiving radiation.[7] Whole-brain irradiation (WBI), in particular, is known to be a significant risk factor for neurocognitive impairment, but other risk factors such as intrathecal methotrexate, tumor location, young age at diagnosis, and hydrocephalus[8–10] have also been linked to impaired neurocognitive outcomes.[11]

For those receiving radiation treatment, radiation dose and volume can affect brain tissue.[12] WBI is associated with worse toxicity-related outcomes than focal radiation with evidence of neurocognitive impairments, such as difficulties in attention, executive functioning, and processing speed.[13–15] Moreover, these treatment-related late effects can have life-long implications for survivors. Neurocognitive functions are important for everyday functioning including work and educational attainment and thus play an important role in QoL.[13,16] However, few studies have investigated the relationship between neurocognitive outcomes, QoL in childhood brain tumor survivors, and associations with symptom burden including sleep disturbances, fatigue, and psychological distress.[17] Such a multi-faceted perspective may yield a more comprehensive picture of survivors' post-treatment QoL and the ongoing burden of late effects that may inform future targets for interventions.

Thus, the aim of the present study was to assess the nature and severity of neurocognitive impairments in a nationwide cohort of five–year survivors of childhood brain tumors and to compare survivors treated with and without radiation. Furthermore, we aimed to evaluate QoL and symptom burden in survivors treated with radiation compared to no radiation and to assess their associations with neurocognitive functions. Finally, associations between neurocognition and tumor location as well as other clinical risk factors, eg, hydrocephalus, time since diagnosis, and age at diagnosis were explored.

Materials and Methods

Data Sources and Study Population

All children diagnosed with a brain tumor between January 1, 1997 and December 31, 2015 were identified in the Danish Childhood Cancer Registry (DCCR) and invited to participate. The DCCR is a nationwide clinical quality database set up with the overall aim of monitoring the quality of childhood cancer care in Denmark.[18] Inclusion criteria for the study population were (1) a confirmed diagnosis of a brain tumor at the age of ≤ 15 years, (2) time since diagnosis >5 years, and (3) age at the time of clinical examination >15 years. We excluded survivors with evidence of recent disease progression ($n = 2$) and survivors with an intraspinal tumor ($n = 15$). All eligible adult and adolescent survivors received an invitation letter and a subsequent reminder approximately 3 months later. If they did not respond to any of the letters, a medical doctor (Anne Sophie L. Helligsoe (ASLH)) attempted to contact the survivor or their parents by phone to inform them about the study. All survivors who agreed to participate underwent study assessments that included a clinical examination, questionnaires, and a neurocognitive evaluation. All assessments were undertaken in the period from August 1st, 2019 to September 1st, 2021.

Measures

Demographic information.—Demographic and socioeconomic information were collected from questionnaires and included gender, educational attainment, yearly income, weekly alcohol consumption, and use of painkillers. Medical information was extracted from medical reports and confirmed in the DCCR and included medical history, age at diagnosis, tumor type, and treatment (surgery, chemotherapy, and/or radiation).

Neurocognitive tests.—Participants underwent neurocognitive assessment with a battery of standardized tests that took approximately 60 min. The different neurocognitive tests examined the following domains: processing speed, sustained attention, attention and working memory, verbal learning and memory, verbal fluency and executive functions (Supplementary Table S1). The tests have been recommended by the International Cognition and Cancer Task Force[19] and were chosen to achieve a comprehensive assessment of different relevant cognitive functions that are known to be impaired in various cancer patients.

Questionnaires.—We assessed QoL using the European Organization for Research and Treatment of Cancer (EORTC) core questionnaire (EORTC QLQ-C30) consisting of 30 questions regarding global QoL, functional scales (physical, role, emotional, cognitive, and social functioning) and symptom scales plus the brain tumor module (BN20).[20] Insomnia severity was assessed with the Insomnia Severity Index (ISI).[21,22] Total scores were interpreted as follows: absence of insomnia (0–7), sub-threshold insomnia (8–14), moderate insomnia (15–21), and severe insomnia (22–28). Self-reported fatigue was measured with The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F).[23] Fatigue severity was defined as: extreme fatigue (0–13), quite a lot of fatigue (14–26), some fatigue (27–39), and no or little fatigue (40–52). Symptoms of anxiety or depression were measured using the Hospital Anxiety and Depression Scale (HADS).[24] A total score of either anxiety or depression at or above 8 indicated a mild (8–10), moderate (11–14), or severe (15–21) case.

Ethical Approval and Storage of Data

The study was approved by the National Health Committee of Research Ethics (# 1-10-72-65-19) and the relevant data protection agency (Central Denmark Region, # 1-16-02-109-19). The study was performed in accordance with the Declaration of Helsinki. If the participant accepted the invitation, written informed consent was obtained. Study data were collected and managed using the secure web–based software platform Research Electronic Data Capture (REDCap) hosted at Aarhus University, Denmark.[25]

Statistical Analyses

For each neurocognitive test outcome, an age-adjusted *z*-score was calculated based on available normative data. A global composite score (GCS) was calculated as an average *z*-score based on *z*-scores from the individual neurocognitive tests. Clinically significant impairment on each test outcome was defined as a *z*-score ≥1.5 in the direction of impairment. Following published guidelines,[19] participants were categorized as having clinically significant cognitive impairment when they evidenced impairment in at least two different cognitive domains.

Demographic and clinical data between participants receiving radiation and those who did not were compared using independent-sample *t*-tests and χ^2 tests. One-sample *t*-tests were used to compare participants' average *z*-score on each test outcome with the normative mean ($z = 0$). Between-group differences in neurocognitive test outcomes were compared with two-sample *t*-tests, eg, for tumor location (supratentorial vs. infratentorial). Multiple linear regression analysis was used to test if hydrocephalus, age at diagnosis, and time since diagnosis predicted GCS.

Correlation analyses were performed to assess the association between GCS and global QoL, insomnia, fatigue, anxiety, and depression. Exploratory analyses of the association between specific cognitive domains, QoL and symptom burden were undertaken. In all analyses, a *P*-value < .05 was considered statistically significant.

Results

Study Participation and Demographic Characteristics

A total of 431 eligible survivors were identified in the DCCR (Figure 1). Of those, 8 had missing addresses. A total of 241 survivors did not respond to our invitations and could not be reached by phone, and 12 declined to participate. A total of 170 accepted the invitation to participate, yielding a participation rate of 40.2%. Apart from a slightly higher frequency of participating females, participants versus non-participants were similar in relation to time since diagnosis, age at diagnosis, and tumor location (Supplementary Table S2).

Of the 170 participants enrolled, 161 (94.7%) completed all assessments, whereas 9 (5.3%) completed questionnaires only. Reasons for not completing all assessments were: parents declined on behalf of their child ($n = 4$); too stressed to undergo testing ($n = 2$); not having the time ($n = 2$); or isolated due to COVID-19 ($n = 1$).

The mean sample age at diagnosis was 9.1 years (95% CI 0.87–15.9), the mean time since diagnosis was 15.1 years (95% CI 5.1–24.6), and the mean age at examination was 24.3 years (95% CI 23.4–25.1). Please see Table 1 for details regarding demographic and clinical data. Overall, 66 participants (41.0%) were still living with their parents. A total of 48 participants (29.8%) were in a relationship, and 13 (8.0%) had children (Table 1). No group differences between participants not treated with irradiation (no-Rx, $n = 102$) and participants treated with radiation (Rx, $n = 59$) were observed for gender, time to diagnosis, time since diagnosis, age at diagnosis, age at assessment, and presence of hydrocephalus. Of the 59 (37%) participants treated with Rx, 55 (93%) were treated with multimodal therapy and 4 (7%) were treated only with Rx. As expected, more children diagnosed between 0 and 4 years of age were in the no-Rx group compared with the Rx-group (13.6% vs. 20.6%, respectively), as radiation is often avoided in young children to protect the developing brain. There were more participants with low-grade astrocytomas represented in the no-Rx group compared with the Rx-group (55.9% vs. 25.4%, respectively) ($P < .01$) and more participants with embryonal tumors represented in the Rx-group (33.9% vs. 1.0%, respectively) ($P < 0.01$).

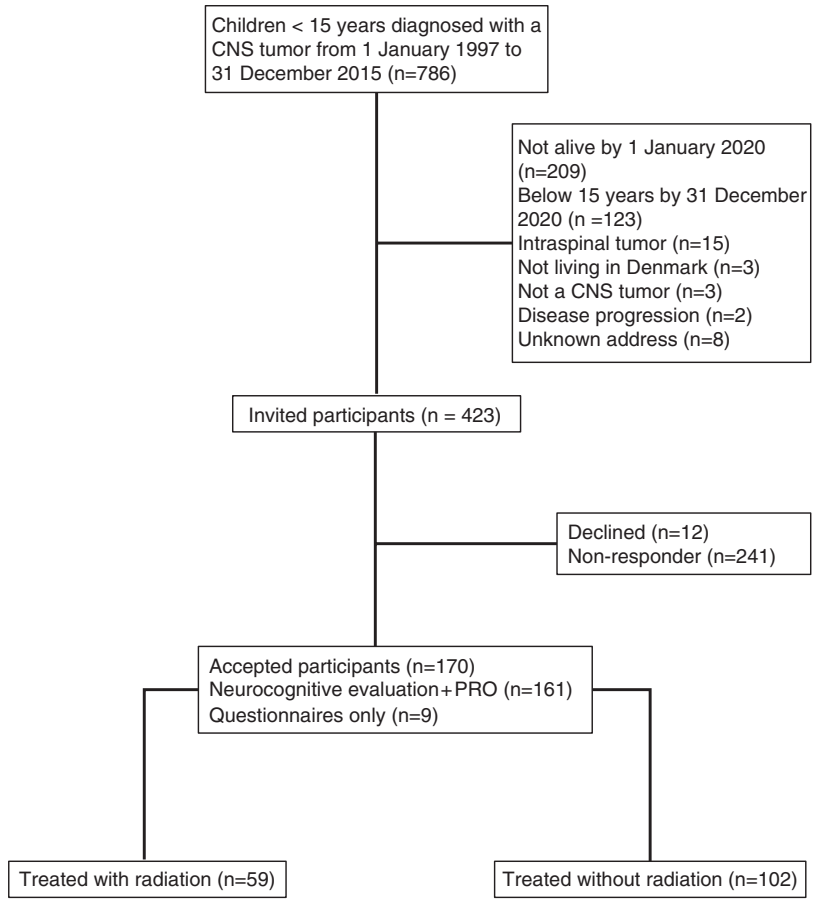
Neurocognitive Function Compared with Normative Data

In total, 107 (66%) survivors had significant overall impairment with the following distribution in the six domains: 17 (10.6%) in two domains and 90 (55.9%) in three or more domains. Of the 54 participants, who did not have an overall impairment, 27 (16.8%) participants evidenced impairments in no domains and 27 (26.8%) in one domain,

Mean *z*-scores for all neurocognitive test outcomes for survivors treated with Rx compared with no-Rx are presented in Table 2. TMT-A, Coding, CCPT detectability (d′), CCPT omissions, CCPT commissions, Digit span, HVLT-R total, HVLT-R delayed, HVLT-R recognition, and TMT-B for all participants were significantly lower than the normative mean ($z = 0$). Figure 2A illustrates mean *z*-scores for all survivors across cognitive tests compared with the normative means of each test.

Associations between Neurocognitive Function and Radiation

Figure 2 illustrates mean *z*-scores for all survivors, survivors treated with surgery alone (no radiation or chemotherapy), survivors treated with Rx vs. no-Rx, and survivors treated with Rx stratified by focal Rx and WBI. The neurocognitive outcome for survivors treated with surgery



*The Danish Childhood Cancer Registry (DCCR) is cross-linked with the Danish Cancer Registry[46] and includes all Danish children diagnosed with a neoplasm according to the International Classification of Diseases version 10 (ICD-10 codes DC00-DD48), who were below 15 years of age at the time of diagnosis.

Figure 1. Flow diagram of children <15 years diagnosed with a CNS tumor in the Danish Childhood Cancer Registry* from January 1, 1997 to December 31, 2005 ($n = 786$).

alone was compared with normative data. Survivors treated only with surgery (n = 88, 54.7%) showed significantly lower scores in all domains except verbal fluency compared to normative data.

As shown in Table 2, survivors treated with Rx (n = 59, 36.6%) evidenced significantly lower scores in the domains of processing speed, sustained attention, attention and working memory, and verbal learning and memory compared to no-Rx ($P < .05$). Survivors treated with WBI (n = 30) suffered from a broad range of impairments especially within processing speed and executive functions with a worse outcome compared to focal Rx (Figure 2, panel D). Survivors treated with focal Rx suffered from impaired sustained attention, attention and working memory, verbal learning and memory, and executive functions compared to normative data, but did not differ on any of the neurocognitive tests compared to no-Rx survivors (Figure 2, panel D).

Association between Neurocognitive Outcomes and Tumor Location

Compared to survivors with a supratentorial tumor, survivors with an infratentorial tumor (n = 81) evidenced poorer performance on Coding (mean z-score –0.17 vs. mean z-score –0.75, $P < .01$) and COWAT Animals mean (z-score 0.03 vs. mean z-score –0.35, P = 0.02) (Supplementary Table S3). After adjustment for WBI, survivors with an infratentorial tumor still had poorer performance in processing speed ($P = .03$).

Associations between Clinical Risk Factors and Neurocognitive Outcome

The results of the multiple regression indicated that hydrocephalus ($\beta = –0.45$, $P < .01$) and younger at age diagnosis (β = 0.04, P = 0.02) significantly predicted a lower GCS,

Table 1. Demographic and CNS tumor characteristics of survivors, who received radiation, either whole-brain irradiation or focal radiation, compared to no-radiation

Characteristics	Focal Rx	%	WBI	%	No-Rx	%	Total	%	*P*-value*
Participants	29	18	30	19	102	63	161		
Sex									
Female	17	59	15	50.	55	54	87	54	.92
Male	12	41	15	50	47	46	74	46	
Time to diagnosis, median days (range)	90	(1–913)	92	(1–730)	60	(1–1460)	61	(1–1460)	.32
Time since diagnosis, mean years (95% CI)	14.6	(12.6–16.7)	16.0	(14.2–17.2)	14.9	(5.1–23.7)	15.1	(5.1–24.6)	.41
Age at cancer diagnosis, mean years, (95% CI)	9.4	(7.8–10.9)	9.6	(8.6–10.6)	9.0	(0.87–15.9)	9.1	(0.87–15.9)	.67
Age at examination, mean years (95% CI)	24.9	(22.0–26.0)	25.6	(23.5–27.8)	23.9	(22.9–25.0)	24.3	(23.4–25.1)	.31
Predisposing syndrome									.52
Neurofibromatosis type 1 or 2	2	7	0	-	8	7	10	6	
Tuberous sclerosis					1	1.0	1	0.6	
Hydrocephalus at presentation	5	17	20	67	25	25	49	30	
CNS tumor characteristics									
Localization of tumor									<.01
Cerebellum	9	31	18	60	42	41	69	43	
Cerebrum	2	7	4	13	26	26	32	20	
Supratentorial central area	1	3	2	7	9	9	12	7	
Hypothalamus or pituitary region	4	14	1	3	13	13	18	11	
Brain stem	7	24	0	-	5	5	12	7	
Optic nerve or chiasma	3	10	0	-	7	7	10	6	
Pineal gland	3	10	5	17	0		8	5	
ICCC3-subgroups									< .01
Ependymoma and choroid plexus tumor	5	17	3	10	6	6	14	9	
Astrocytoma	15	52	0	-	57	56	72	45	
Intracranial embryonal tumor	0	-	20	67	1	1	21	13	
Other gliomas	3	10	0	-	2	2	6	4	
Other specified intracranial neoplasms	2	7	1	3	24	24	27	17	
Unspecified intracranial neoplasms	0	–	0	–	2	2	2	1	
Germ cell tumors	4	14	6	20	2	2	11	7	
Unclassified	0	–	0	-	7	7	8	5	
CNS tumor treatment									
Chemotherapy	12	41	26	87	4	4	42	26	<.01
No chemotherapy	17	59	4	13	98	96	119	74	
Surgery	23	79	30	100	91	89	144	89	.92
No surgery	6	21	0	-	11	11	17	11	
Demographics									
Living with parents	11	38	11	37	44	43	66	41	
In a relationship	10	35	8	27	30	29	48	30	
Has one or more children	2	7	2	7	9	9	13	8	
Educational attainment									
Primary school	11	38	19	63	32	31	62	39	

Table 1. Continued

Characteristics	Focal Rx	%	WBI	%	No-Rx	%	Total	%	*P*-value*
High school education	5	17	3	10	29	28	37	23	
Vocational training	2	7	3	10	15	15	20	12	
Short higher education	2	7	2	7	6	6	10	6	
Medium-term further education	4	14	0	-	9	9	13	8	
Bachelor	1	3	0	-	4	4	5	3	
Long higher education	4	14	2	7	6	6	12	7	
PhD or researcher	0	-	1	3	1	1	2	0.01	
Yearly income									
USD 0–7620	8	28	8	27	22	22	38	24	
USD 7621–15241	6	21	3	10	24	24	33	20	
USD 15242–30482	10	34	13	43	33	32	56	35	
USD 30283–45723	2	7	4	13	13	13	19	12	
USD 45724–60964	0	-	0	-	2	2	2	0.01	
USD 60965–76205	2	7	1	3	5	5	8	5	
USD > 76206	1	3	1	3	3	3	5	3	
Employed	16	6	14	47	63	62	93	58	
Alcohol consumption									
0–7 units/week	29	100	28	93	84	82	141	88	
7–13 units/week	0	-	1	3	15	15	16	10	
14–21 units/week	0	-	0	-	2	2	2	0.01	
>21 units/week	0	-	1	3	2	2	2	0.01	
Currently treated for epilepsy	1	3	5	17	14	14	20	12	
Use of endocrinological replacement therapy	6	21	18	60	8	8	32	20	
Use of painkillers									
Daily	2	7	3	10	6	6	11	7	
Weekly	2	7	5	17	14	14	20	12	
Monthly	12	41	6	20	30	29	48	30	
Rarer	13	45	16	53	52	51	81	50	

Rx (radiation), WBI (whole-brain irradiation), no-Rx (not treated with radiation), **P*-value refers to survivors receiving radiation compared to survivors who did not

whereas time since diagnosis (β = –0.01, P = 0.57) was not identified as a predictor.

Quality of Life and Symptom Burden

Total scores on HADS, FACIT-F, and ISI in all survivors, survivors treated with Rx or no-Rx, as well as survivors only treated with surgery are shown in Table 3. Differences between survivors treated with Rx and no-Rx on EORTC-QLQ-C30-BN20, HADS, FACIT-F and ISI are reported in Table 4. Participants treated with Rx reported a lower mean global QoL score on the EORTC-QLQ-BN20 (mean global QoL 71.8, 95% CI [66.5–77.2]) compared to participants treated with no-Rx (mean global QoL 78.7, 95% CI [75.4–82.1] P = .02). No between-group difference in global QoL scores between focal Rx and WBI was found (P = .50). Furthermore, survivors treated with Rx reported reduced physical (P < .01) and social functioning (P < .01) and more fatigue (P = .01) compared to survivors treated with no-Rx.

A total of 22 (13%) participants evidenced clinical levels of insomnia and 3 (1.8%) had severe insomnia (Supplementary Table S5). A total of 65 (39%) participants reported fatigue to some extent on the FACIT–F (some fatigue n = 41, quite a lot of fatigue n = 24). A total of 38 (23%) participants evidenced anxiety and 11 (6%) participants evidenced signs of depression. No difference (P > .05) between the Rx and no-Rx group was observed for insomnia, fatigue, anxiety, or depression.

Associations between Neurocognitive Function, Quality of Life and Symptom Burden

The correlations between neurocognitive outcome and global QoL, insomnia, fatigue, anxiety, and depression were investigated. A trend was found in survivors, with

Table 2. Mean *z*-scores of neurocognitive outcomes for participants, who received radiation (Rx) compared to no-radiation (no-Rx) by cognitive domain

Domain	Test	Rx, mean (95% CI), *n* = 57–58	*Impairment within domain, *n* (%)	no-Rx, mean (95% CI), *n* = 99–100	*Impairment within domain, *n* (%)	*P*-value
Processing speed	TMT-A	–1.43 (–2.15 to –0.71)	22 (38)	–0.90 (–1.29 to –0.50)	28 (28)	.16
	Coding	–0.77 (–1.07 to –0.48)		–0.29 (–0.50 to –0.07)		<.01
Sustained attention	CCPT HRT	–0.07 (–0.34 to 0.19)	40 (69)	0.36 (0.22–0.50)	51(51)	<.01
	CCPT d′	–1.03 (–1.33 to -0.73)		–0.95 (–1.20 to –0.71)		.69
	CCPT omissions	–1.50 (–2.0 to –0.99)		–1.24 (–1.60 to –0.88)		.41
	CCPT commissions	–0.28 (–0.57 to 0.003)		–0.45 (–0.68 to –0.21)		.40
Attention and working memory	Digit span	–0.61 (–0.86 to –0.37)	12 (21)	–0.26 (–0.45 to –0.06)	7 (7)	.03
Verbal learning and memory	HVLT-R total	–1.31 (–1.63 to –0.95)	44 (76)	–1.03 (–1.27 to –0.80)	61 (61)	.17
	HVLT-R delayed	–1.69 (–2.04 to –1.33)		–1.22 (–1.50 to –0.95)		.04
	HVLT-R recognition	–1.44 (–1.81 to –1.08)		–1.04 (–1.33 to –0.75)		.09
Verbal fluency	COWAT Letter S	0.04 (–0.43 to 0.50)	6 (10)	–0.04 (–0.24 to 0.17)	8 (8)	.74
	COWAT Animals	–0.32 (–0.61 to –0.03)		–0.07 (–0.27 to 0.13)		.14
Executive functions	TMT-B	–1.80 (–2.64 to –0.95)	22 (38)	–1.13 (–1.54 to –0.71)	33 (33)	.11

*Impairment within domain is defined as a *z*-score ≤ 1.5 in one of the tests
Trail Making Test Part A (TMT-A), Wechsler Adult Intelligence Scale version 4 (WAIS-IV), Conners' Continuous Performance Test version 3 (CCPT), Hit Reaction Time (HRT), d (detectability), Hopkins Verbal Learning Test - Revised (HVLT-R), Controlled Oral Word Association Test (COWAT), Trail Making Test Part B (TMT-B)
P-value refers to survivors receiving radiation compared to survivors who did not

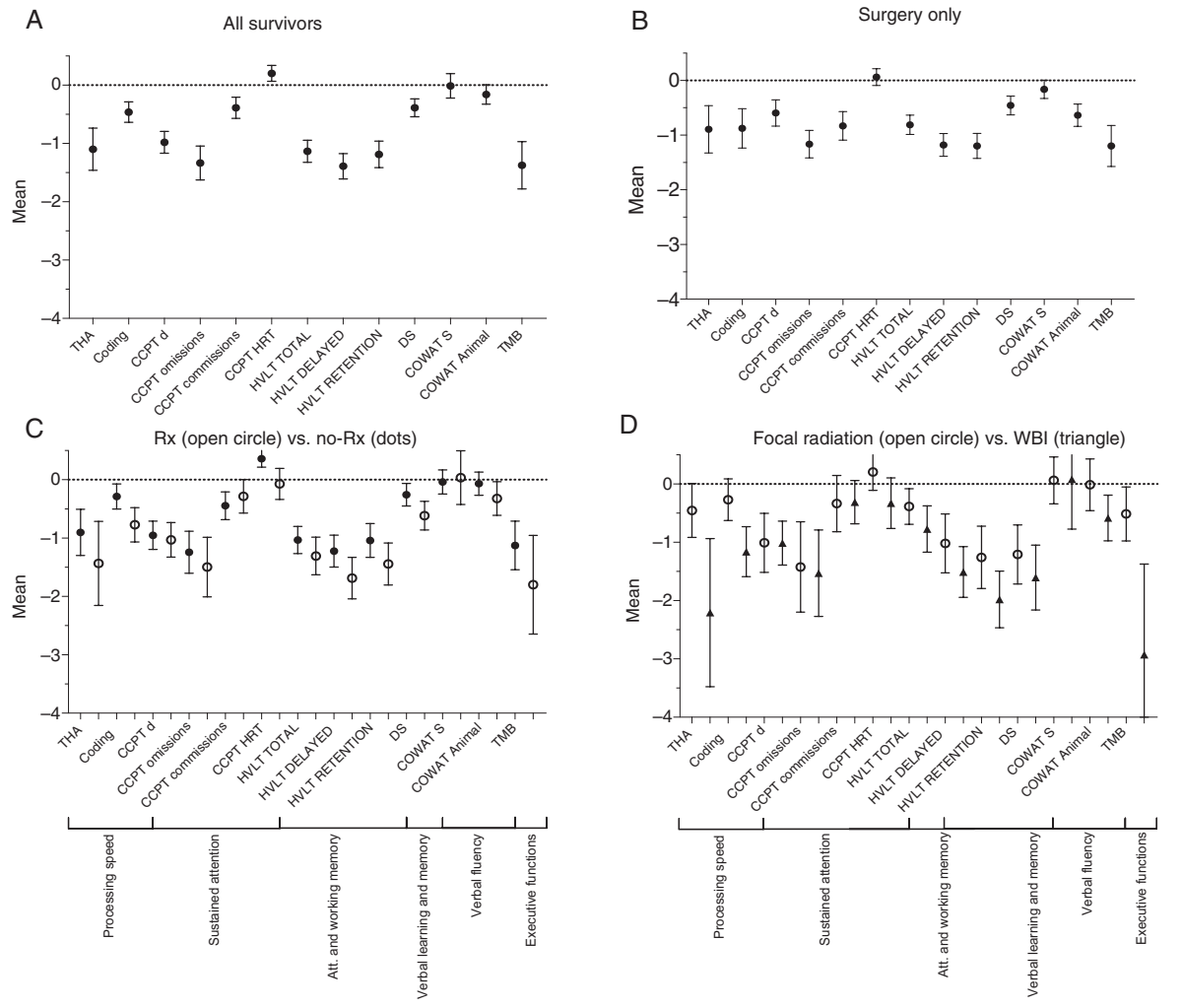


Figure 2. Neurocognitive mean *z*-scores of (A) all survivors, (B) survivors treated with surgery alone, (C) survivors treated with radiation (Rx) compared to no radiation (no-Rx), and (D) survivors treated with focal radiation (focal Rx) and whole brain irradiation (WBI) in the neurocognitive tests and their related domains. Trail Making Test Part A (TMT-A), Wechsler Adult Intelligence Scale version 4 (WAIS-IV), Conners' Continuous Performance Test version 3 (CCPT), Hit Reaction Time (HRT), d (detectability), Hopkins Verbal Learning Test - Revised (HVLT-R), Controlled Oral Word Association Test (COWAT), Trail Making Test Part B (TMT-B)

higher fatigue scores significantly correlated with lower GCS (r = 0.17, P-value .03). No associations between GCS and global QoL (r = 0.14, P = .09), insomnia (r = –0.04, P = .59), anxiety (r = 0.03, P = .71) or depression (r = –0.04, P = .60) were found.

Associations between specific cognitive domains, QoL, and symptom burden were explored. Processing speed (r = 0.182, P = .02), attention and working memory (r = 0.173, P = .03), and sustained attention (r = 0.170, P = .045) were correlated with poorer QoL. Attention and working memory (r = 0.240, P = .002), verbal fluency (r = 0.172, P = .03) and sustained attention (r = 0.274, P < 0.001) were correlated with more fatigue. Moreover, sustained attention (r = 0.182, P = .02) was correlated with insomnia. Finally, scores of anxiety and depression were not correlated to specific cognitive domains.

Discussion

While previous studies tend to examine neurocognitive functions, QoL, and symptom burden in separate studies, we included all outcomes in this study to assess the potential impact of neurocognitive impairment on QoL and symptom burden. These components are inextricably linked, as cognitive functions play a critical role in the development of psychosocial behavior affecting QoL.[26] To our knowledge, this is the first study to report the association of neurocognitive impairment with QoL and symptom burden in childhood brain tumor survivors. The survivors in this study were identified in a national registry, treated in a country with equal access to healthcare and received the

Table 3. Depression, anxiety, fatigue, and insomnia in all survivors, survivors treated with surgery only, survivors not treated with radiation (no-Rx), and survivors treated with radiation (Rx).

	Surgery only		No-Rx		Rx		All survivors	
	n *n* = 88	%	*n* *n* = 106	%	*n* *n* = 64	%	*n* *n* = 170	%
Depression/anxiety								
No depression/anxiety	82/73	93.2/83.0	103/86	97.2/81.1	57/47	89.0/73.4	157/132	92.4/77.6
Mild depression/anxiety	4/12	4.5/13.6	2/18	1.9/17.0	6/10	9.4/15.6	9/28	5.3/16.5
Moderate depression/anxiety	2/1	2.3/1.1	1/1	0.9/0.9	1/4	1.6/6.3	4/5	2.4/2.9
Severe depression/anxiety	0/2	-/2.3	0/1	–/0.9	0/3	–/4.7	0/5	–/2.9
Fatigue								
No or little fatigue	56	63.6	62	58.5	35	54.7	103	60.6
Some fatigue	25	28.4	27	25.5	13	20.3	41	24.1
Quite a lot fatigue	8	9.1	8	7.5	16	25.0	24	14.1
Extreme fatigue	0	–	0	–	0	–	0	–
Insomnia								
Absence of insomnia	52	59.1	60	56.6	42	65.6	104	61.2
Sub-threshold insomnia	26	29.5	29	27.4	13	20.3	43	25.3
Moderate insomnia	10	11.4	11	10.4	7	10.9	19	11.2
Severe insomnia	1	1.1	1	0.9	2	3.1	3	1.8

Table 4. Mean global quality of life, insomnia severity, fatigue, and psychological distress in participants treated with radiation compared with no irradiation

Questionnaire scores	All survivors (*n* = 169) mean	95% CI	Rx (*n* = 64) mean	95% CI	No-Rx (*n* = 105) mean	95% CI	*P*-value
Global QoL, 0–100	76.1	73.2–79.0	71.8	66.5–77.2	78.7	75.4–82.1	.03
Physical functioning	86.8	84.2–89.4	80.3	75.4–85.2	90.8	88.1–93.5	<.01
Social functioning	83.5	79.8–87.2	74.1	66.9–81.3	89.2	85.5–92.9	<.01
Fatigue (EORTC-QLQ-C30-BN20)	32.6	28.9–36.3	38.4	31.5–45.4	29.1	25.0–33.2	.01
Insomnia, 0–28	7.1	6.2–8.0	7.3	5.6–8.9	7.1	5.9–8.1	.79
Fatigue 0–52 (FACIT–F)	40.1	38.4–41.7	38.1	34.7–41.5	41.3	39.6–43.0	.07
Anxiety (*n*, %)	38	(23)	17	(27)	20	(20)	.28
Depression (*n*, %)	11	(6)	7	(11)	3	(3)	-

Rx (treated with radiation), no-Rx (not treated with radiation), QoL (quality of life), EORTC-QLQ-C30-BN20 (quality of life), FACIT–F (fatigue questionnaire).

same diagnostic protocols during the same time period. Survivors were, on average, 15 years post-diagnosis, and undertook comprehensive assessments that included neuropsychological evaluations, self-report questionnaires, as well as clinical information from medical records. We found that 66% of the survivors showed overall neurocognitive impairment, which is in alignment with prevalence rates between 40% and 100% reported in other studies.[13,27,28] We applied a rigorous recruitment process to limit selection bias and used gold standard objective cognitive tests, which is important in this population as the participants' personality and emotional characteristics might affect the results of self-reported data.[29]

Neurocognitive decline[30] and especially processing speed are known to be reduced in the years after treatment with radiation.[31,32] Our study corroborates this finding, particularly as treatment with WBI affected processing speed. Reduced processing speed is particularly important to identify as processing speed influence executive functions and thereby academic skills.[33] Survivors with an infratentorial tumor also showed slower processing speed as well as poorer verbal fluency. This finding is consistent with infratentorial tumors being associated with postoperative cerebral mutism syndrome[34] with impaired speech up to a year after treatment and highlights that verbal fluency may

be an area of vulnerability for those treated for an infratentorial tumor.

Interestingly, survivors treated with focal radiation exhibited no difference in neurocognitive outcomes compared to survivors, who were not treated with radiation. This finding emphasizes the importance of choosing a relevant control group. We conducted a within-cohort comparison with survivors not treated with radiation and other studies have used survivors with low-grade astrocytomas for comparison.[35] If we had only compared survivors treated with focal radiation with normative data, we might have overestimated the negative effect of radiation.

Survivors treated with surgery only also evidenced poorer neurocognitive outcomes than normative expectations although less than in survivors treated with radiation. Survivors treated with surgery only displayed impairment in all but one domain (ie, verbal fluency), which is consistent with other research.[35] This finding highlights that even survivors treated with surgery only may be vulnerable to neurocognitive impairment.

Attention deficits and especially difficulties with sustained attention have previously been reported in survivors of childhood brain tumors.[15] Compared to normative data, survivors treated with or without radiation in this study exhibited inattentiveness with no difference between the two groups. A meta-analysis confirmed that survivors of childhood brain tumors exhibited lower abilities to sustain attention than the norm, but no differences in reaction time were found.[36] We identified that survivors were impaired when they should actively inhibit an inappropriate response as seen in children with attention deficit hyperactive disorders.[37] An additionally interesting finding was that survivors who had received radiation in our study actually had faster reaction times on a sustained attention task than those who had not received radiation, but their accuracy was worse, suggesting an inhibition problem. Consistent with this finding, previous studies have related attention-deficits to radiation–induced white matter damage.[38]

Risk factors of poor neurocognitive outcome such as hydrocephalus, younger age at diagnosis, longer time since diagnosis, and tumor location have been identified by others.[39,40] We found that hydrocephalus and younger age at diagnosis were also risk factors for the poor neurocognitive outcome. However, we could not confirm longer time since diagnosis as an independent risk factor. The pathogenesis of how hydrocephalus contributes to neurocognitive decline has not been clarified.[41] The pressure from hydrocephalus may have an acute effect on neurocognitive structures of the brain, however, a long-term effect cannot be ruled out, as our findings show that hydrocephalus is still a risk factor in survivors 15 years after diagnosis.

Analyzing QoL and symptom burden, 39%, 23%, 13%, and 6% of the survivors were burdened with fatigue, anxiety, insomnia, and depression, respectively. Furthermore, survivors reported reduced global QoL, particularly in physical and social functioning, which was significantly lower for survivors treated with radiation. We hypothesized that neurocognitive impairment would be related to decreased measures of QoL and symptom burden; however, we were not able to confirm this. Previously, executive functions assessed with proxy reports have been related to health–related QoL,[42] though this method of assessing neurocognitive functioning was not used in our study. In the future, it may be important to assess self-reported and proxy reports of the influence of cognitive functioning on daily living as well as through the use of neuropsychological tests. Although the patients treated with radiotherapy experienced more neurocognitive challenges and reduced QoL, these patients also had, in general, more aggressive malignant disease than patients treated with surgery alone. The impact of the primary disease may therefore have contributed to this finding. In addition, we need to identify other risk factors for reduced QoL and neurocognitive dysfunction such as psychosocial factors (eg, children with higher trait anxiety[43] and families lower in support and higher in conflict[44]), as radiation treatment exposure was insufficient to explain the entire survivorship experience.

Major strengths of this study include the identification of participants from the national registry that captures the entire Danish population. Furthermore, we included all brain tumor diagnoses according to the ICCC-3 and were not limited to a single tumor subtype. The survivors were assessed in a multi-faceted way including data from a performance-based assessment, clinical examination, and medical records.

However, there were also limitations to the study. First, we included a relatively small and heterogenous sample of survivors treated with focal radiation, which may have limited our ability to detect differences in neurocognitive outcomes between survivors treated with or without radiation. Second, the cross-sectional design of neurocognitive data collection limited our ability to assess causal associations. Third, multiple comparisons of many risk factors increased the risk of statistically significant trends occurring by chance. However, we did select clinical variables a priori for statistical analyses. Finally, we did not evaluate self-reported cognitive functioning, which may have provided more information about the cognitive functions that patients experience as being important, and may have had stronger associations with QoL and symptom burden—associations often found in other studies of cancer survivors.[45]

In conclusion, this study highlights that neurocognitive impairment is a significant problem for a majority of childhood brain tumor survivors, especially among those who received radiation treatment. A significant proportion of survivors also experienced clinically significant insomnia, fatigue, depression, and anxiety. Survivors, who received radiation were also more vulnerable to neurocognitive impairment and lower global QoL than those who did not receive radiation. Altogether, these results show that radiation is a risk factor for the poorer neurocognitive outcome, QoL and greater symptom burden, but the relationship is more complex than previously presumed. It is well-known that children diagnosed with a brain tumor and treated with radiation often have more severe diseases. Despite neurocognitive impairment some survivors' QOL and symptom burden were not impaired, suggesting that they were adequately coping with any deficits. Survivors capable of transitioning from vulnerability during the cancer course to

resilience in their life afterward, tend to have the ability to better adapt to new circumstances.[46] Further studies on how individuals cope with impairments are warranted. Furthermore, the fact that survivors treated with surgery only are neurocognitively affected emphasizes that these patients also need follow-up care. Tiered models of care for neurocognitive surveillance have been suggested.[47] Future clinical studies as well as follow-up care that includes neurocognitive assessments, together with QoL and symptom burden assessments are indicated.

Supplementary material

Supplementary material is available online at *Neuro-Oncology* (http://neuro-oncology.oxfordjournals.org/).

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Author Contributions

ASLH designed the study, collected, analyzed, and interpreted the data; wrote and edited the manuscript. YL and LW interpreted the data, critically reviewed the statistical analyses and the manuscript. LTH, LK, JFW, HH, and AA designed the study, interpreted the data, critically reviewed the statistical analyses and the manuscript.

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