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Rate of Radiation-Induced Microbleed Formation on 7T MRI Relates to Cognitive Impairment in Young Patients Treated with Radiation Therapy for a Brain Tumor

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Abstract

Background: Radiation therapy (RT) is essential to the management of many brain tumors, but has been known to lead to cognitive decline and vascular injury in the form of cerebral microbleeds (CMBs).

Purpose: In a subset of children, adolescents, and young adults recruited from a larger trial investigating arteriopathy and stroke risk after RT, we evaluated the prevalence of CMBs after RT, examined risk factors for CMBs and cognitive impairment, and related their longitudinal development to cognitive performance changes.

Methods: Twenty-five patients (mean 17 years, range:10–25 years) underwent 7-Tesla MRI and cognitive assessment. 19 patients were treated with whole-brain or focal RT 1-month to 20-years prior, while 6 non-irradiated patients with posterior-fossa tumors served as controls. CMBs were detected on 7T susceptibility-weighted imaging (SWI) using semi-automated software, a first use in this population.

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Results: CMB detection sensitivity with 7T SWI was higher than previously reported at lower field strengths, with one or more CMBs detected in 100% of patients treated with RT at least 1-year prior. CMBs were localized to dose-targeted brain volumes with risk factors including whole-brain RT (p=0.05), a higher RT dose (p=0.01), increasing time since RT (p=0.03), and younger age during RT (p=0.01). Apart from RT dose, these factors were associated with impaired memory performance. Follow-up data in a subset of patients revealed a proportional increase in CMB count with worsening verbal memory performance (r=−0.85,p=0.03).

Conclusions: Treatment with RT during youth is associated with the chronic development of CMBs that evolve with memory impairment over time.

Keywords

cerebral microbleeds; radiation therapy; brain tumors; ultra-high field magnetic resonance imaging; cognitive outcome

1 Introduction.

Brain tumors are the most common solid cancer in children younger than 15 years old.[1] Radiation therapy (RT) remains integral to the treatment of pediatric brain tumors, having significantly improved disease prognosis for common malignant tumors such as medulloblastomas: in average-risk disease, the 5-year survival for these tumors is now at 70–80%.[2,3] Elevated 5-year survival rates have also been achieved through the use of RT as a stand-alone therapy in the treatment of germinomas.[4] Despite having contributed to the overall survival benefit experienced by patients, such therapeutic approaches are associated with long-term morbidities, remaining a key challenge in patient outcome and motivating alternative approaches such as chemotherapy combined with reduced RT dose for the treatment of germinomas.[4] Because patients in this young group live well into adulthood, the impact of treatment on development and quality of life are important considerations.

RT in particular is a key contributor to long-term treatment effects including cognitive decline and vascular injury.[5–7] Compared to standalone surgery and chemotherapy approaches, RT has been associated with higher degrees of cognitive impairment, and specifically whole-brain RT (WBRT) has been related to a decline in multiple intelligent quotient points per year following treatment.[9–11] Both the risk and severity of cognitive impairment increase with younger age during RT, higher RT doses, and larger irradiated volumes such as a whole-brain versus a focal approach.[12] In children, irradiating certain regions of the brain such as the hippocampus has also been linked to cognitive impairment.[13]

One manifestation of radiation-induced vascular injury is tiny hemosiderin deposits in the brain called cerebral microbleeds (CMBs). CMBs can be best detected with magnetic resonance imaging (MRI) using a technique known as susceptibility-weighted imaging (SWI) as early as 8 months following treatment.[14] Previous studies have shown that CMBs first appear in the high-dose brain areas, and increase in number over time, more rapidly in individuals treated at a younger age, with higher RT doses delivered to larger brain volumes.[15–20]

Incidence rates for CMBs after RT and their clinical relevance, however, remain elusive, in part explaining why available automated tools have not been adopted in standard practice to routinely measure and report CMB burden. Rates ranging from 44–90% have been reported based on follow-up times between 4 and 46 years.[17–22] While one cross-sectional study linked RT-induced CMBs to impaired executive function,[21] suggesting CMBs as a marker of impairment, the longitudinal relationship between RT-induced CMBs and cognition has not been fully explored. Still, this association is supported by evidence from other patient populations, as CMBs have previously been related to the cognitive decline experienced by healthy aging adults, stroke patients, and patients with neurodegenerative diseases.[23–29] Technical limitations in prior studies further warrant a more thorough investigation of the link between CMBs, treatment details, and cognition. There has been a lack of sensitivity and variability in imaging methods, little consideration for patient and treatment heterogeneity, and the use of manual techniques for analysis based on visual inspection. Detection of CMBs from magnitude images or SWI acquired with shorter echo times[30] and at clinical field-strengths (1.5, 3.0T) has been shown to substantially limit the detection sensitivity compared to using SWI and state-of-the-art ultra-high field (7T) MRI technology recently approved for clinical use. With increases in field-strength, better signal-to-noise ratio, anatomical resolution, and susceptibility contrast can be achieved, making 7T SWI ideal for visualizing CMBs.[31] Combined with computer aid, CMBs can be detected with even higher accuracy, as manual detection of CMBs from MR images has also been shown to have reduced sensitivity.[32]

In this study we used 7T SWI with consistent imaging acquisition parameters, quantitative methods, and a computerized battery of cognitive evaluations, to report on the prevalence of CMBs in 25 brain tumor patients treated during youth with either WBRT, focal RT or without RT. We examine risk factors for CMBs and cognitive impairment, and relate longitudinal development of CMBs to changes in cognitive performance.

2 Materials and Methods.

2.1 Patient Recruitment

Patients imaged at 7T in this study were recruited from a larger multisite brain tumor study using lower-field clinical images to investigate arteriopathy and stroke risk in children with brain tumors treated with RT. Institutional review board approval and parental or patient informed consent were obtained prior to participation. Inclusion criteria included treatment at age < 25 years, completion of treatment at least 1 month prior to enrollment, age > 6 but < 30 at time of assessment, and ability to undergo an MRI without sedation. Recruitment of patients treated with RT for a brain tumor outside the supratentorial brain was prioritized to minimize the effects of the tumor itself on outcome measures. The majority of patients were treated with a uniform whole brain dose plus a radiation “boost” to the tumor bed within the posterior fossa or to the whole posterior fossa itself. Others received a focal RT strategy including either whole-ventricular RT (WVRT) where a uniform dose was delivered to the ventricles followed by a “boost” to the tumor bed (specific to patients treated for a germinoma), or a true non-uniform dose the tumor bed and surrounding tissue (in the case of two patients with supratentorial tumors). A subset of non-irradiated patients with tumors

outside of supratentorial brain were also recruited as a control group. Exclusion criteria for both groups consisted of known vasculopathy prior to initiation of RT, the presence of a shunt within the brain, medications affecting neurocognitive status (e.g. antipsychotics), and co-morbid disorders that affect cognition (e.g. developmental delay prior to brain tumor diagnosis) as determined by the treating physician.

2.2 Imaging

All patients were scanned on a 7T GE (General Electric) Healthcare scanner with a 2-channel transmit and 32-channel receive head coil. SWI images were acquired via a novel multi-slab, multi-gradient echo sequence (with flow compensation along readout, repetition time (TR)/echo time (TE)/TE2/TE3/TE4=40/2.7/10.5/13.2/20.9ms, flip-angle (FA)=20°, with 1mm slice thickness, 0.5 mm in-plane resolution, 24cm field of view (FOV), and in-plane ARC parallel imaging with an acceleration factor of R=3 and 16 autocalibration lines).[33] T1-weighted anatomical images were also acquired via an inversion recovery, spoiled gradient recalled sequence (IR-ISPGR with inversion time/TR/TE = 600ms/6s/2ms, FA=8, with 1mm isotropic resolution, 25.6cm FOV, and acceleration factor of R=2.2).A subset of patients returned for follow-up imaging using the same protocol at least 1-year after the initial visit.

2.3 Cognitive Assessment

Cognitive performance was evaluated using a battery of computerized cognitive tests (Cogstate, Inc.; Newhaven, CT) chosen to elucidate impairments in multiple cognitive domains including: attention (Identification Task (IDN)), association learning and visual memory (Continuous Paired Associate Learning Task (CPAL)),psychomotor function (Detection Task (DET)), executive function (Groton Maze Learning Task (GML)), verbal memory & learning (International Shopping List Task (ISL), Delayed Recall for ISL (ISRL)), and working memory (One Back Test (ONB)). Numerical outputs from each neurocognitive test (e.g. total number of errors) were converted to normalized age-appropriate z-scores using mean performance scores of healthy control subjects from the Cogstate database. A global score was generated for each patient by averaging domain-specific z-scores. Follow-up cognitive testing was performed during the follow-up MRI visit.

2.4 Image Analysis

An expert rater blinded to all clinical information, detected and segmented CMBs from SWI images using a novel semi-automated CMB detection and fully-automated CMB segmentation algorithm.[34,35] The algorithm has increased sensitivity and inter-rater agreement over other computer-based methods, providing a more accurate characterization of CMB burden.[35] CMB burden was measured as the total number of CMBs in each patient; the total volume of CMBs in each patient was also evaluated in parallel. An atlas-based anatomical parcellation scheme (Montreal Neurological Institute) was used to partition the brain and quantify the spatial distribution of CMBs.

2.5 Statistical Analysis

Kruskal-Wallis and Wilcoxon rank sum tests compared CMB burden and cognitive scores across the different patient groups (WBRT, focal RT, or no RT). Univariate and multivariate regressions evaluated risk factors for CMBs and cognitive impairment, including RT strategy (whole versus focal), time since RT, age during RT, dose, and max dose (with “boost”).The rate-of-change in CMB burden was compared to the change in cognitive scores using Pearson correlations. The rate metrics were computed as the difference in CMB count (or test z-score) at baseline and follow-up divided by time to follow-up in years. A Bonferroni multiple comparisons correction was applied where appropriated.

3 Results.

Twenty-five patients total (52% female, mean 17 yrs, range 10–25 yrs) were recruited including: 12 patients treated with WBRT, 7 with focal RT (including WVRT), and 6 non-irradiated control patients. Time since RT ranged between 1 month to 20 years. Ten patients returned for follow-up imaging and cognitive testing, on average 1.69 years (range, 0.96 – 3.75) after the first visit. Two patients’ imaging data were unusable due to motion-artifacts. Table 1 summarizes patient details.

3.1 Prevalence & Distribution of CMBs

One or more CMBs were detected in all patients treated with RT at least 1-year prior, whereas no CMBs were detected in the non-irradiated control patients. Patients treated with WBRT versus focal RT had significantly more CMBs (p=0.008, Figure 1A). CMBs developed in brain areas targeted by RT; they were distributed throughout the brain after WBRT, while localized to tissue surrounding the ventricles after focal WVRT (Figure 1B). Of the >700 CMBs detected in patients treated with WBRT, majority were localized to the anterior white matter, followed by the gray matter of the occipital, temporal and frontal lobes. These findings were the same whether evaluating CMB burden as the total number or volume of CMBs.

3.2 Risk Factors for CMB Development

WBRT (p=0.05), increased time since RT (p=0.03), younger age during RT (p=0.01), and greater RT dose (p=0.01) were associated with increased CMB burden (Table 2, Figure 1C). No effects of biological sex, race, maximum dose, hydrocephalus or diabetes were identified. The same results were found when the analysis was repeated with patients treated for a medulloblastoma only (n=11).

3.3. Factors associated with memory impairments

Compared to non-irradiated controls, patients exposed to radiation performed much worse on the ISL verbal memory task ($p_{focalRT}$=0.003, p_{WBRT}=0.01, Figure 2A). Corrected p-values were not significant. Analogous to the risk factors for CMBs, increased time since RT (p_{ISL}=0.02, p_{ISRL}=0.09) and younger age during RT (p_{ISL}=0.02, p_{ISRL}=0.08) were associated with worse performance on the verbal memory and learning tasks, a trend that followed when repeated with only medulloblastoma cases (Table 3). WBRT (p_{ONB}=0.03) and younger age during RT (p_{ONB}=0.07) were uniquely associated with poorer performance

on the ONB working memory task. The effects of WBRT on working memory can be visualized in Figure 2A. Figure 2B illustrates the relationship between memory, time since RT, and age during RT.Despite overlap between risk factors, we found no direct cross-sectional relationships between CMBs and cognition in our data.

3.4 Longitudinal Relationship between CMBs and Cognition

New CMBs were identified on serial imaging in all 6 irradiated patients with usable data (Figure 3A), while the 2 non-irradiated control patients maintained an absence of CMBs. Global performance worsened at follow-up in all patients treated with WBRT (n=4), apart from the one who was treated at a relatively older age of 12 (Figure 3B). The remaining patients, either non-irradiated (n=2) or treated with focal RT (n=3), performed better or slightly worse at follow-up. In those patients who had CMBs and useable imaging data (n=6), we found that, relative to other patients, CMBs developed in the individual patient at a rate which was similar to their decline in memory performance (Figure 3C; association learning and visual memory: $R_{CPAL}=-0.47$, $p_{CPAL}=0.35$; verbal memory and learning: $R_{ISL}=-0.76$, $p_{ISL}=0.13$, $R_{ISRL}=-0.85$, $p_{ISRL}=0.03$).

3.5 Patient examples

Patient examples further underscore the relationship between CMBs, treatment details, and cognition. Two patients (Table 1, #5 and #8) treated with WBRT for a medulloblastoma at the age of 7, presented with 206 and 330 CMBs, at 15 and 5 years post-treatment, respectively. Neither had co-existing neurological conditions and both underwent standard resection and chemotherapy. However, patient #5 received a lower uniform WBRT dose (23.4 versus 36 Gy), indicating why he had 60% fewer CMBs than patient #8 despite being 10 years further out from treatment.

Two additional patients (#12 and #14) treated with focal WVRT for a germinoma at the age of 9, presented with 47 versus 4 CMBs at 10 and 13 years post-treatment, respectively. Both underwent standard biopsy and chemotherapy, and were diabetic, however their clinical profiles differed in that patient #12 was treated with a higher radiation “boost” (45 versus 40.5 Gy) and had hydrocephalus that required an endoscopic third ventriculostomy at the time of RT.

Other patients (#1 and #4) who were treated with high dose WBRT (≥36 Gy) at 3 and 6 years old, 19 years prior, were visibly impaired and had difficulty cooperating during imaging, rendering their images unusable due to significant motion artifacts, though the presence of some CMBs could be appreciated. The patients who performed the worst on tasks evaluating executive function (GML), psychomotor function (DET) and working memory (ONB), included patients #1, #4, #5, and #8, whom were imaged 19, 19, 15, and 5 years after WBRT, respectively. They were all treated for a medulloblastoma and either had unusable images due to motion (#1 and #4) or presented with the highest number of CMBs in the study (#5 and #8).

4 Discussion.

Although RT remains a standard practice in pediatric neuro-oncology and has improved disease prognosis for many young patients with brain tumors, its long-term side effects pose significant challenges. To date, few groups have investigated RT-induced CMBs in young patients. While its agreed that the presence and accumulation of CMBs are a side effect of RT, variable and relatively low incidence rates have been reported due to the use of less reliable MR images acquired at lower field strengths.[19–21, 31] We evaluated CMBs using 7T SWI images with enhanced susceptibility contrast and high resolution, thereby enabling their detection in 100% of patients treated at least 1-year post-treatment. This greatly exceeds the cumulative incidences reported in Roddy et al.'s large cohort study[21], which were as low as 10.8% after 1-year and under 50% at 5-years post-RT, based on less sensitive imaging and manual counting of CMBs. A maximum of 49 CMBs were detected in any one patient in their study, whereas, using 7T SWI, more than 200 CMBs were detected in two patients. Despite a much lower sample size in our study, using similar methods presented here, an incidence rate of 100% at 1-year post-treatment was also reported in more than 100 adult brain tumor patients.[36]

In agreement with previous work[21], we found CMB development to be spatially influenced by the RT strategy. In the case of WBRT, our results suggest that specific brain regions may be more likely to develop CMBs. This includes inferior brain areas near the tumor site that are disrupted by resection and receive the highest radiation dose. Further, the frontal lobe has been shown to mature subsequent to other brain regions, and may therefore be hypersensitive to RT with respect to the surrounding brain tissue.[37] With a more accurate measure of CMB burden based on 7T SWI, our multivariate analysis confirms risk factors for CMBs after RT including larger brain volume exposure to radiation, younger age during RT, and increased time since RT. Consistent with work by Neu et al.[17], we also observed a relationship between CMB burden and RT dose.

In the absence of imaging data, these same risk factors have been reported by numerous investigations of cognitive status after RT. [7–12,21,22] We evaluated performance on CogState's comprehensive battery, used to a great extent in prior studies,[21,38,39] and found that larger brain volume exposure to radiation, younger age during RT, and increased time since RT to be associated with significant decline in memory function. In a recent study of adult stroke patients, Christ et al.[40] also reported memory-associated functions to be most affected in patients with CMBs, a relevant finding given the high risk for stroke after RT[40]. Despite an overlap between risk factors for CMBs and memory impairment, we found no direct cross-sectional relationships been the two. While Roddy et al.[21] reported a relationship between CMB burden and executive function measured by CogState's GML task, we were unable to replicate this finding due to our inability to densely capture neurocognitive outcomes in the range of 5 to 15 years post-RT. Nonetheless, our worst performers on the GML tasks were those with many CMBs or motion-affected data (see section 3.4), the latter of whom we believe harbor a significant number of CMBs as a result of their unfavorable treatment conditions. The same individuals also performed the worst on the ONB task, a finding that agrees with Heitzer et al's[39] results from a prospective longitudinal study of cognition before versus 3-months after RT for a medulloblastoma.

Our longitudinal analysis suggests a potentially meaningful temporal relationship between CMB development and memory impairment that may warrant further study. However, given that impairments were also observed in non-irradiated patients after surgery and chemotherapy,[42] biological factors confounding neurocognitive outcome (e.g. loss of white matter integrity[43]) must be considered in further interrogation of this relationship. Nonetheless, collective evidence from our study, previous studies in patients with brain tumors[14–21], and studies in other patient populations[23–29] suggest some clinical relevance of CMBs. It remains unclear, however, whether SWI and quantification of CMB burden will have a future role in the management of young brain tumor patients.

The most significant limitation of the study is the small cohort size due to challenges with enrollment and loss of follow-up. As mentioned, this limited our ability to densely capture data in the range of 5 to 15 years post-RT and resulted in the recruitment of some patients with supratentorial tumors outside our preferred inclusion criteria. Although we achieved high-resolution images at 7T in clinically acceptable scan times, image volume coverage was limited to the supratentorial brain, where we hypothesized CMBs would have the most prominent effect on cognition. This restricted imaging FOV led to slight variations in coverage in the most superior and inferior axial slices of the brain and limited the ability to characterize vascular injury in the posterior fossa, the primary tumor site for most patients. Finally, we recognize that reproducibility of findings from this study are challenged by the limited availability of 7T scanners. Although 7T MRI is used here as an exploratory research tool to elucidate the prevalence and clinical relevance of CMBs, our group has been working on translating our sequence and enhancing the sensitivity of CMB detection through developing post-processing tools that can increase CMB contrast at lower field strengths, making their quantification clinically assessible.

In conclusion, 7T SWI is highly sensitive to CMBs, enabling their detection in 100% of patients treated with RT at least 1-year prior. Risk factors for CMBs and cognitive impairment overlap and are consistent throughout the literature, with our study suggesting new insights to a longitudinal relationship between the two, particularly in memory-associated functions.

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Abbreviations:

CMBs	cerebral microbleeds
RT	radiation therapy
WBRT	whole-brain RT
WVRT	whole-ventricular RT

SWI susceptibility-weighted imaging

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Highlights.

1. CMB detection sensitivity with 7T SWI was higher than reported at 1.5T and 3T
2. 7T SWI revealed CMBs in 100% of patients treated with RT ≥1 year prior
3. Memory performance was most affected after RT
4. The rate of CMB development overtime correlated with the rate of memory decline
5. Age, dose, time and brain volume exposed to RT influenced outcome

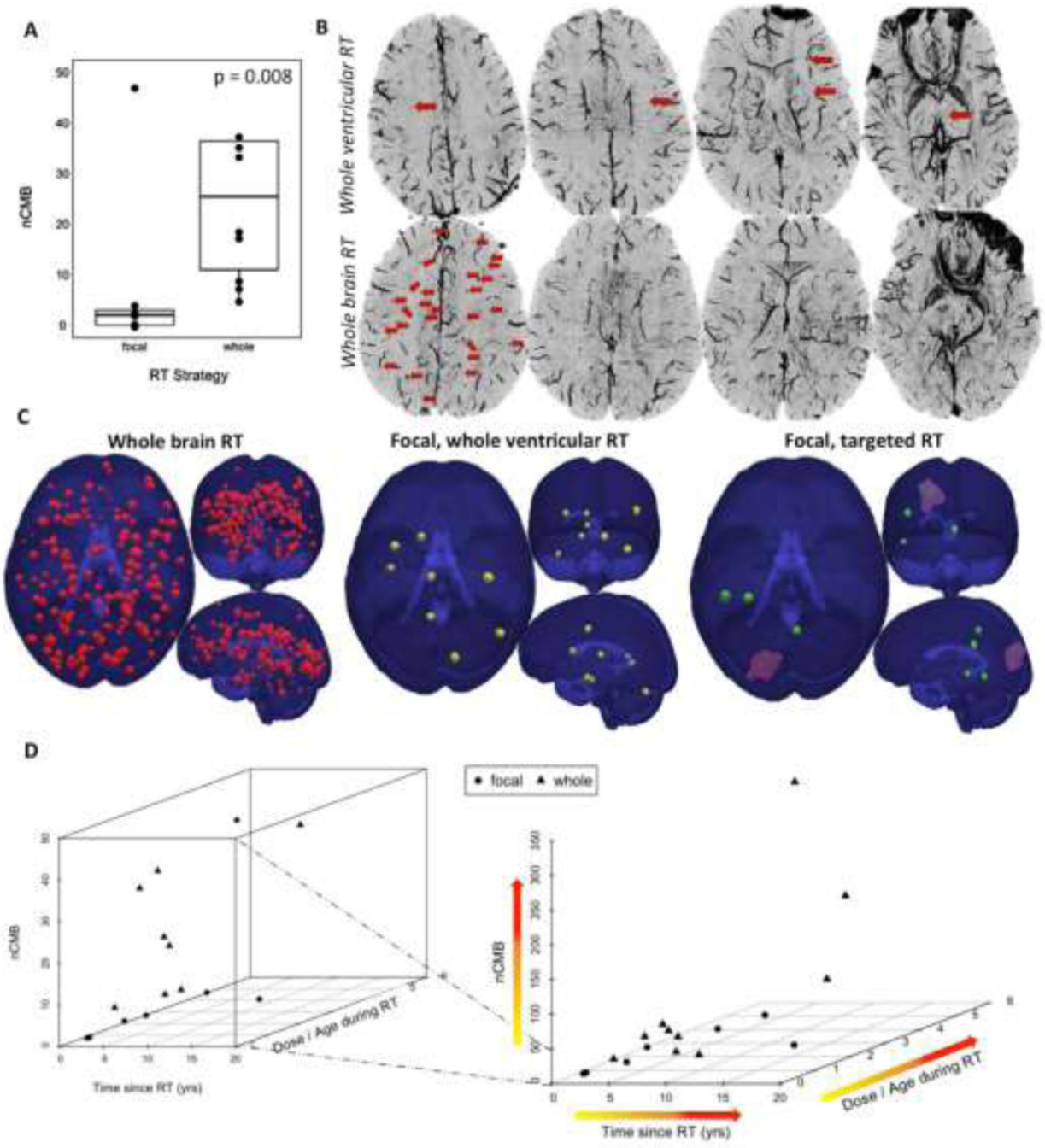

Figure 1. Risk factors for the development of CMBs after RT.

Patients treated with whole brain RT presented with significantly more CMBs than patients treated with focal RT including whole ventricular RT (A). When comparing two age-matched patients, one treated with whole brain RT 15 years prior, and the other treated with focal RT 13 years prior, striking differences in CMB burden are seen (B). A composite of patients' CMBs in (C) (excluding some patients with many CMBs for better visualization), illustrates localization of CMBs to the dose-targeted brain areas.In addition to treatment

strategy, greater dose, younger age during RT, and greater time since RT contributed to the most severe cases of chronic CMB development (D).

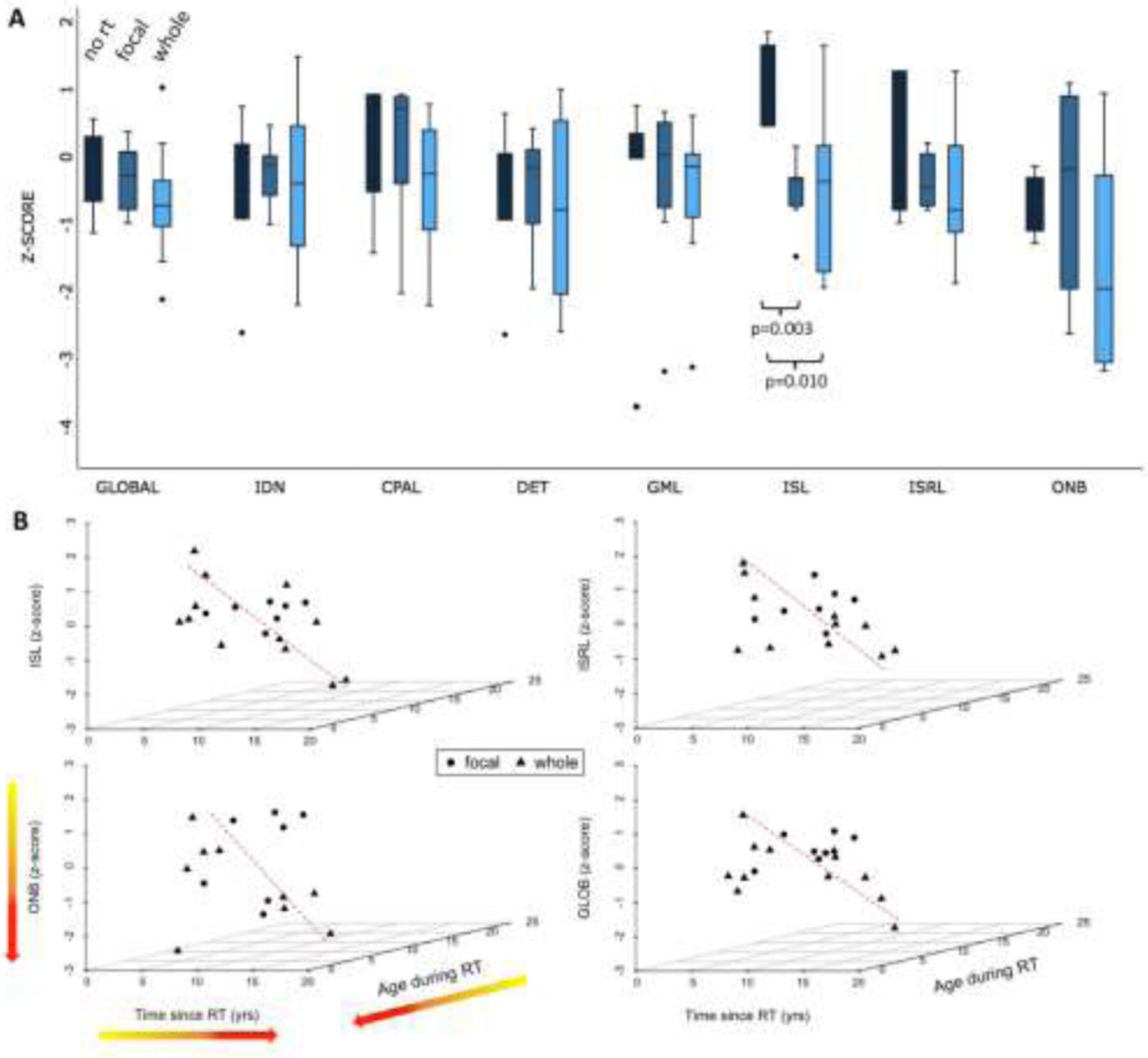

Figure 2. Risk factors for memory impairment after RT.

Performance on a verbal memory task different significantly between patients treated without RT versus with focal or whole brain RT (A). The most severe memory impairments were observed in patients treated at younger ages, and imaged further out from treatment (B). *Cognitive domains:* attention (IDN), association learning and visual memory (CPAL), psychomotor function (DET), executive function (GML), verbal memory and learning (ISL, ISRL), working memory (ONB).

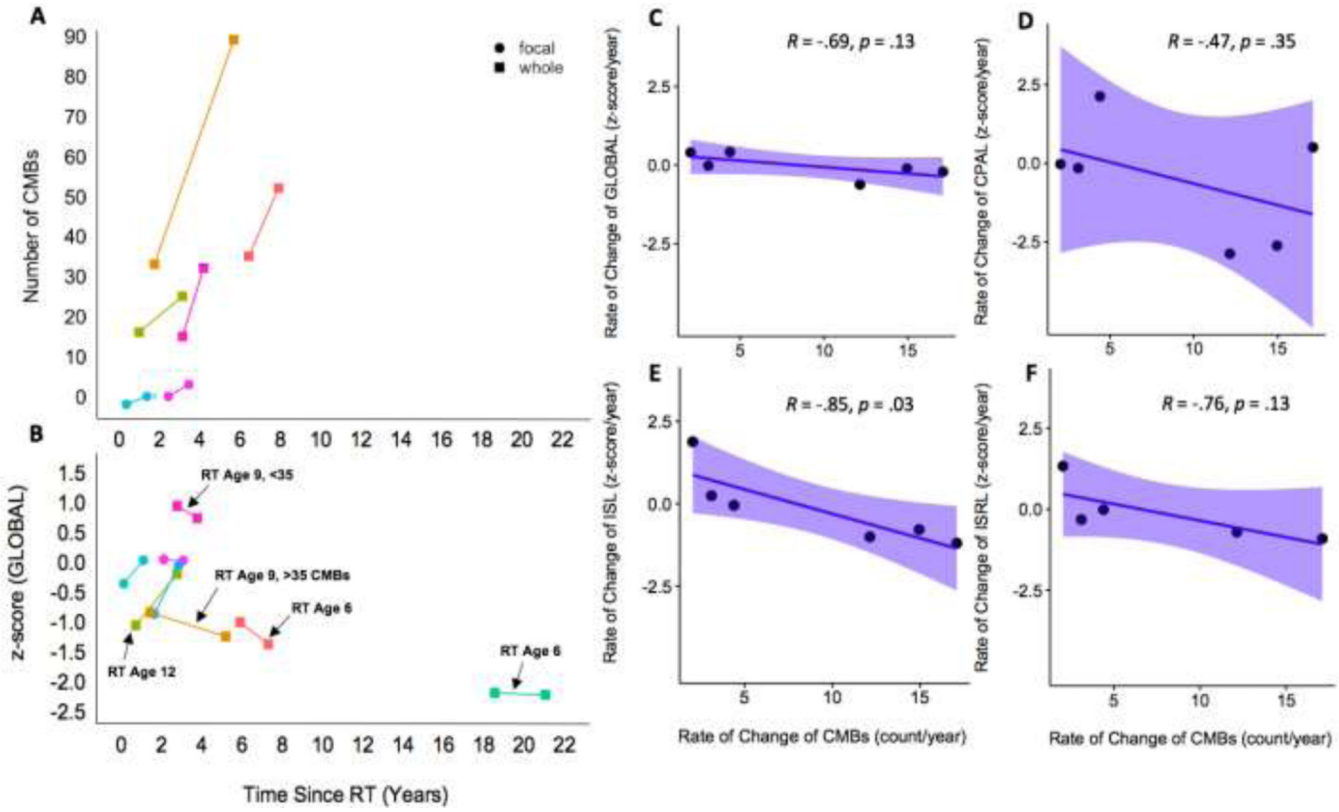

Figure 3. Serial changes in CMB burden and cognitive performance.

Of the 10 patients imaged serially (8 treated with RT, 2 treated without RT), 6 RT-treated patients had usable imaging data, and presented with new CMBs at follow-up (A). All but one patient treated with whole brain RT at the age of 12, worsened in global performance (denoted by the arrows and annotations) (B). The remaining patients treated with focal RT or no RT (not shown) performed better or slightly worse at follow-up (B). The rate of change in global performance, and performance on memory-domain tasks, correlated with and the rate of increase in CMB development (C-F). *Cognitive domains:* association learning and visual memory (CPAL), verbal memory and learning (ISL, ISRL).

Table 1.

Patient Demographics.

Patient	Sex	Race	Cancer Type	Tumor location	RT	Age (yrs)			RT dose, max (Gy)	nCMBs		Surgery	Chemo	Other Dx
						RT	1st MRI	2nd		1st MRI	2nd			
1	M	hispanic	medu	p. fossa	wb	3	22	--	37, 53.5	n/a	--	gtr × 4	vincristine	--
2	F	white	medu	p. fossa	wb	18	22	--	36, 55.8	7	--	biopsy	cisplatin, cyclophosphamide,vincristine	--
3	M	white	medu	p. fossa	wb	14	22	--	23.5, 54	9	--	gtr	carboplatin, CCNU, cytoxan, VP-16,vincristine	--
4*	M	white	medu	p. fossa	wb	6	25	27	36, 55	n/a	n/a	gtr	carboplatin, CCNU, vincristine	hypertension
5	M	white	medu	p. fossa	wb	7	22	--	23.4, 55.8	206	--	gtr	CCNU, cisplatin,vincristine	--
6*	M	white	medu	p. fossa	wb	12	12	14	36, 54	18	27	str	carboplatin,vincristine	--
7	M	white	medu	p. fossa	wb	13	15	--	23.4, 54	33	--	gtr	CCNU, cisplatin, cytoxan, dendritic cell vaccine, stem cell,vincristine	hydro cephalus
8	F	asian	medu	p. fossa	wb	7	12	--	36, 55	335	--	gtr	carboplatin, cisplatin, cyclophosphamide,vincristine	--
9	F	white	medu	p. fossa	wb	23	24	--	36, 59.4	5	--	str	cisplatin, cyclophosphamide,vincristine	--
10*	F	white	medu	p. fossa	wb	9	11	14	23.4, 54	35	91	gtr	carboplatin, CCNU,cisplatin, cyclophosphamide, cytoxan,vincristine	--
11*	F	white	medu	p. fossa	wb	4	10	11	23.4, 54	37	54	gtr	carboplatin, CCNU,cisplatin, vincristine	--
12	M	asian	germ	ventricle	wv	9	19	--	24, 45	47	--	ETV, biopsy	carboplatin, VP-16	DI, hydro cephalus
13	M	white	germ	ventricle	wv	22	22	--	18, 30	0	--	str	carboplatin, etopside, ifosfamide	DI
14	F	white	germ	ventricle	wv	9	22	--	24, 40.5	4	--	biopsy	carboplatin, VP-16	DI
15*	F	other	germ	ventricle	wv	12	14	15	18, 30	2	n/a	biopsy	carboplatin, VP-16	DI
16*	F	asian	germ	ventricle	wv	24	24	25	18, 33	0	2	biopsy	carboplatin, VP-16	--
17*	M	white	PPT	p. fossa	wb	9	12	13	23.4, 54.9	17	34	gtr, ETV	cisplatin, cyclophosphamide	hydro cephalus, stroke
18*	M	white	ganglio	occipital	focal	15	17	18	59.4, 59.4	2	5	gtr	vemurafenib	--
19	M	black	astro	parietal	focal	22	22	--	59.4, 59.4	0	--	gtr	--	--
20*	F	white	oligo	temporal	--	--	15	16	--	0	0	gtr	everolimus	--
21	F	white	JPA	p. fossa	--	--	18	--	--	0	--	gtr	--	--
22	F	white	JPA	p. fossa	--	--	13	--	--	0	--	gtr	--	hydro cephalus
23	M	asian	JPA	p. fossa	--	--	16	--	--	0	--	gtr	--	--

Patient	Sex	Race	Cancer Type	Tumor location	RT	Age (yrs)			RT dose, max (Gy)	nCMBs		Surgery	Chemo	Other Dx
						RT	1st MRI	2nd		1st MRI	2nd			
24*	F	hispanic	JPA	p. fossa	--	--	14	17	--	0	0	ETV, biopsy	--	hydro cephalus
25	F	white	JPA	p. fossa	--	--	16	--	--	0	--	gtr	lenalidomide, lomustine, temozolomide	hydro cephalus

*returned for follow up imaging and neurocognitive testing

medu = medulloblastoma, germ = germinoma, PPT = pineal parenchymal, ganglio = anaplastic ganglioglioma, astro = pleomorphic xanthoastrocytoma, oligo = oligodendroglioma, JPA = juvenile pilocytic astrocytoma, p.fossa = posterior fossa, wb = whole brain, wv = whole ventricular, n/a = data affected by motion, gtr = gross total resection, str = sub-total resection, ETV = endoscopic third ventriculostomy, DI = diabetes insipidus

Table 2.

Risk factors for microbleed development following radiation therapy (RT).

Cohort	Risk factor *dependent variable: nCMB*	Univariate Poisson		Multivariate Poisson	
		IRR (95% CI)	P-value	IRR (95% CI)	P-value
All irrradiated patients (n=19)	**RT Strategy**, whole vs. focal	8.93 (0.44–180)	0.17	8.88 (1.20–74.7)	0.05 •
	Time since RT, each additional year	1.14 (0.97–1.35)	0.13	1.14 (1.03–1.26)	0.03 *
	Age during RT, each additional year	0.77 (0.65–0.92)	0.01 *	0.79 (0.68–0.93)	0.01 *
	RT dose, each additional Gy	1.00 (0.92–1.08)	0.98	1.11 (1.03–1.19)	0.01 *
	Max RT dose (w/ boost), each additional Gy	1.07 (0.93–1.22)	0.38	--	--
Medulloblastoma (n=11)	**Time since RT**	1.14 (0.96–1.35)	0.19	1.18 (1.05–1.32)	0.03 *
	Age during RT	0.82 (0.67–1.01)	0.09 •	0.81 (0.70–0.93)	0.03 *
	WBRT dose	1.04 (0.89–1.21)	0.64	1.17 (1.07–1.28)	0.01 *
	Max RT dose (w/ boost)	1.00 (0.52–1.91)	0.99	--	--

*.05 significance level

•.1 significance level

nCMB = total number of microbleeds, CI = confidence interval, Gy = gray, WBRT = whole brain RT

Table 3.

Factors associated with memory impairment following radiation therapy (RT).

Cohort	Dependent variable	Risk factor	Multivariate Poisson	
			IRR (95% CI)	P-value
All irrradiated patients (n=19)	ISL	**RT Strategy**, whole vs. focal	0.66 (0.28–1.58)	0.37
		Time since RT, each additional year	0.90 (0.82–0.97)	0.02 *
		Age during RT, each additional year	0.88 (0.81–0.97)	0.02 *
		RT dose, each additional Gy	0.98 (0.95–1.01)	0.28
	ISRL	**RT Strategy**	0.70 (0.31–1.59)	0.41
		Time since RT	0.93 (0.85–1.01)	0.09 •
		Age during RT	0.92 (0.84–1.00)	0.08 •
		RT dose	1.01 (0.98–1.04)	0.57
	ONB	**RT Strategy**	0.17 (0.04–0.70)	0.03 *
		Time since RT	0.94 (0.82–1.08)	0.38
		Age during RT	0.86 (0.75–1.00)	0.07 •
		RT dose	0.98 (0.93–1.03)	0.49
Medulloblastoma (n=11)	ISL	**Time since RT**	0.89 (0.79–1.00)	0.09 •
		Age during RT	0.89 (0.77–1.02)	0.13
		WBRT dose	0.96 (0.87–1.06)	0.43
	ISRL	**Time since RT**	0.90 (0.80–1.00)	0.10
		Age during RT	0.88(0.78–1.00)	0.09 •
		WBRT dose	1.02(0.93–1.12)	0.67

*.05 significance level

•.1 significance level

CI = confidence interval, ISL = international shopping list, ISRL = delayed recall for ISL, ONB = one back test

Cognitive domains: verbal memory and learning (ISL, ISRL), working memory (ONB)