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Original Article

Radiation-induced vascular changes in the intracranial irradiation field in medulloblastoma survivors: An MRI study

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ABSTRACT

Background and purpose: While survival times after treatment of medulloblastoma are increasing, little is known about radiochemotherapy (RCT)-induced cerebrovascular changes. High resolution vessel wall imaging (VWI) sequences are an emerging tool for the evaluation of cerebrovascular diseases. We performed VWI in medulloblastoma long-term survivors to screen for late sequelae of RCT.

Material and methods: Twenty-two pediatric medulloblastoma survivors (mean age 25.8 years (10–53 years); 16.3 years (mean) post primary RCT (range 1–45 years)) underwent 2D VWI–MRI. Vessel wall thickening, contrast enhancement and luminal narrowing were analyzed. The findings were correlated with the patients' radiation protocols.

Results: Vessel wall changes were observed the intracranial internal carotid artery (ICA) and the vertebrobasilar circulation (VBC) in 14 of 22 patients (63.6%). In multivariate analysis, time after RCT (OR = 1.38, $p < 0.05$) was strongest independent predictor for development of vessel wall alterations. The dose of radiation was not a relevant predictor.

Conclusions: With longer follow-up time intracranial vessel wall changes are observed more frequently in medulloblastoma survivors. Thus VWI is a useful tool to monitor vessel wall alterations of cranially irradiated patients, creating the prerequisite for further treatment of late sequelae.

Medulloblastoma (MB) is a primary malignant embryonal tumor (WHO Grade IV) of the CNS arising infratentorially at the fourth ventricle or in the cerebellum, at a median age of 5–7 years. Accounting for 12–30%, MB is a common childhood CNS tumor. Treatment decisions and prognosis are based on the modified Chang Staging System [1] extended by a number of other factors like age, completeness of resection, histological subtype and genetic markers [2]. A multimodal therapy approach including surgery, combined chemotherapy and radiotherapy is the cornerstone of treatment. Given the propensity of medulloblastoma to disseminate via cerebral spinal fluid (CSF), radiotherapy of the craniospinal axis has been standard practice for over 50 years. This involves the use of craniospinal irradiation (24–36 Gy) with boost to the posterior fossa/primary tumor bed (54–60 Gy) [3]. Due to the overall improvements in treatment there has been an increase in survival over the past 20 years [3] with the population of long-term survivors growing and with a rise in the appearance of therapy-induced long-term effects. It is therefore not only important to improve survival, but also to maintain quality of life [2]. Long-term survivors may suffer from significant late effects, such as cognitive decline, endocrine deficits, hearing impairment, secondary malignancies [3] and different (cerebro-) vascular diseases [4,5]. The platter includes radiotherapy-induced cavernomas [4], micro bleedings (hemosiderin deposits) [4] and atherosclerotic lesions of the extracranial internal carotid arteries [6].

Carotid artery disease is a progressive, usually adult-onset, vascular disease, which has been reported to occur rarely in non-irradiated individuals younger than 50 years of age [7]. Current

Abbreviations: CE, contrast enhancement; CIMIT, carotid intima media thickness; CSF, cerebrospinal fluid; ICA, internal carotid artery; ICAD, intracranial atherosclerotic disease; MB, medulloblastoma; RCT, radiochemotherapy; RCVS, reversible cerebral vasoconstriction syndrome; VBC, vertebrobasilar circulation; VWI, vessel wall imaging.

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understanding of radiation-induced carotid artery disease is primarily based on adult studies. Prospective studies have demonstrated extracranial internal carotid artery stenosis progress at a higher rate in irradiated patients than in non-irradiated controls [8]. Also a tenfold increase in carotid-related strokes has been reported among head and neck cancer patients treated with high-dose neck irradiation compared to the general population [7,9]. Adult follow-up studies provide valuable information, but only little information is available on young adult survivors of childhood cancer [5,10].

Vessel wall imaging (VWI) is an emerging tool for evaluating intracranial artery disease [11]. The superior soft-tissue contrast of high-resolution VWI sequences opens up the opportunity to visualize early atherosclerotic vessel wall alterations despite the relative thinness of intracranial vessel walls. Even though different VWI protocols were used [11–13], multiple publications have shown that 2D VWI techniques performed in-plane perpendicular to the plane of the vessel lumen, are well suited to detect vessel wall pathologies [14]. Analysis of vessel wall thickening, T2 signal characteristics and contrast enhancement, due to a high in-plane resolution and low slice thickness, are utilized for disease differentiation in cerebrovascular diseases like intracranial atherosclerotic disease (ICAD), reversible cerebral vasoconstriction syndrome (RCVS), cerebral artery vasculitis or moyamoya disease [14]. Intracranial atherosclerotic plaques are frequently eccentric in morphology and show varying degrees and patterns of enhancement as well as mixed T2-weighted lesion signal intensities [11]. However, there may be an overlap in imaging appearances [11,15].

This study evaluated cerebrovascular vessel wall alterations within the irradiation field of former pediatric medulloblastoma patients imaged through high-resolution MRI.

Materials and methods

Patient recruitment

Study procedures were approved by the resident ethic committee at the University of Mainz. From the clinical database of the University Medical Centre of Mainz 91 patients with histologically confirmed medulloblastoma (from 1960 to 2014) were identified. Patients between 3 and ≤21 years at the age of diagnosis have been included. Children under the age of 3 years at the age of diagnosis were excluded from the present analysis, as different therapy regimes, avoiding or at least delaying craniospinal radiation, have been used [16].

Patients suitable for the study had to have completed craniospinal irradiation at least one year before inclusion; as early atherosclerotic changes were detected at least 1-year post radiation therapy in ultrasound based studies [17]. From these 66 candidates (mean age at diagnosis 7.5 ± 3.4 years (range 3–17 years; 30 female) 16 had to be excluded because of death, 6 due to loss of follow up and 19 because of active or passive refusal. The remaining twenty-five medulloblastoma survivors were prospective participants to take part in the study. Nevertheless, three patients were excluded as they were not able to undergo MRI at 3.0 Tesla. Finally, 22 patients were included in this study (Fig. 1).

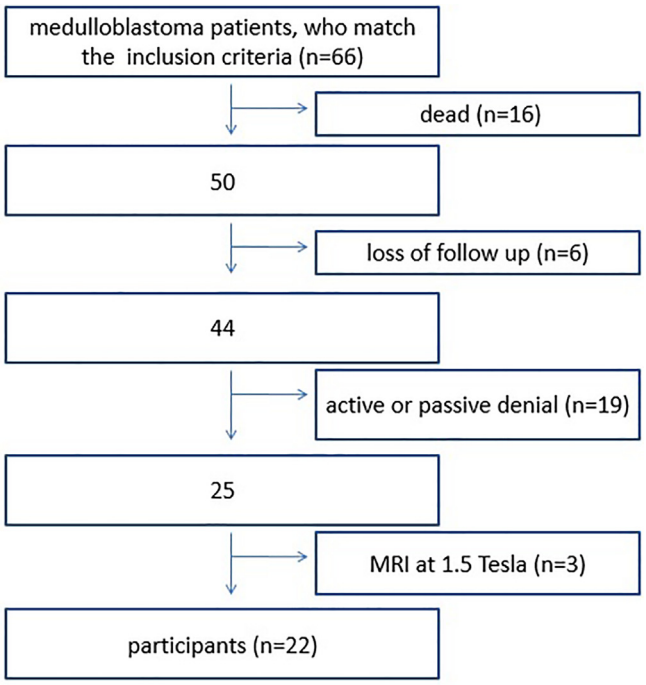

Fig. 1. Flow chart showing the recruitment process of patients with histologically confirmed medulloblastoma (between 1960 and 2014) matching the inclusion criteria.

Demographic and clinical variables

Diagnosis and treatment related information was abstracted from patients' medical records. Radiotherapy parameters (whole head dose and boost dose to the posterior fossa/tumor site, fractionation) were abstracted from the patient's radiation oncology chart and if available from the aria/helax radiation information system.

For further analyses the radiation dose to the posterior fossa was divided into 4 subgroups: 23.4–30 Gy; 30.1–40 Gy; 40.1–50 Gy; ≥50.1 Gy. Clinical and demographic data included age at primary tumor-diagnosis, age at radiotherapy, age at MR scan, gender, smoking habit, and BMI.

Imaging protocol

All scans were obtained using a 3.0 Tesla whole-body scanner (Magnetom Skyra, Siemens, Erlangen, Germany) with a 20-channel combined head/neck coil. MR images were acquired between June 2015 and April 2016. The scan protocol included a standard 3D TOF-MRA, with a matrix of 384 × 365, FoV of 200 × 181 mm and section thickness of 0.50 (reconstructed), which was centered in the Circle of Willis for lumenographic identification of any stenosis. Additionally, three pre- and postcontrast (contrast agent: gadoterate meglumine, Dotarem, Guerbet, Villepinte, France) high-resolution magnetic resonance vessel wall images of the Circle of Willis were implemented.

High-resolution VWI included one axial T2-weighted turbo spin echo sequence and two axial T1-weighted turbo spin echo sequences with and without contrast agent. This part of the protocol was designed to evaluate medium and large-vessels: vertebrobasilar circulation (VBC) with basilar artery (BA), V4 segment of vertebral arteries (VA) and proximal part of the posterior cerebral artery (PCA) as well as intracranial internal carotid artery (ICA). MRI parameters for the T2 und T1 VWI images were as follows:

- 2D T2 (acquisition time 05:07 minutes): 23 slices, slice thickness 2 mm, 0.4 mm gap (TR/TE = 5000 ms/89 ms), matrix = 512 × 358, FOV 220 × 220 mm; voxel size = 0.4 × 0.4 × 2 mm.
- 2D non-contrast and contrast T1 (acquisition time 06:21 min): 18–23 slices, slice thickness 2 mm, 0.1 mm gap (TR/TE/TI = 1170–1270 ms/14 ms/850 ms), matrix = 512 × 410, FOV 220 × 220 mm; voxel size = 0.4 × 0.4 × 2 mm.

The TR/TE/TI parameters provided a black-blood technique. Due to the small size of each section, it was not practical to cover the entire brain in a clinically acceptable time; therefore an imaging slab about 3.7–5.4 cm thickness was selected.

Image analysis

Images were prospectively analyzed and interpreted on a Sectra RIS/PACS viewer (Sectra AB, Linköping, Sweden). A mixed quantitative and qualitative examination was performed by 2 experienced neuroradiologists (S.K.; Y.T.) blinded to clinical data. The readers reviewed lumen narrowing (stenosis) on TOF-MRA and vessel wall characteristics/alterations on VWI. This was done twice, with a minimum time period between the two readings of 8 weeks, by S.K. in order to allow the calculation of the intra-reader analysis, and once through Y.T. to calculate inter-reader reproducibility. The images were analyzed blinded to any patients' data, including name and age. Finally, both readers read the images together for a consistent result. This consistent result was used for further statistical tests.

Following characteristics of the intracranial vessels were analyzed:

- Location of the pathology: intracranial ICA and VBC;
- The character of vessel wall thickening (eccentric vs. circumferential vs. combined);
- The presence of contrast enhancement (CE) in the vessel wall:

The pattern of contrast enhancement was defined as concentric when CE in the artery wall was circumferential (Fig. 2) and as eccentric when CE was observed only in parts of the vessel wall (Fig. 3).

Analysis of the radiation doses to the intracranial internal carotid artery and the vertebrobasilar circulation

Estimation of the maximum radiation doses to the intracranial sections of the intracranial ICA and the VBC was performed cooperatively by one experienced radiation oncologist (M.S.) and one experienced neuroradiologist (S.K.) blinded to clinical data. For patients treated in 2001 and later, the radiation doses were estimated on the basis of the complete 3D Dose distribution. The slice thickness of the corresponding CT simulation was 1 cm in most cases. Image quality did not allow for direct visualization of intracranial vascular structures. For patients treated earlier than 2001 the radiation doses were estimated on the basis of individual simulation films and portal images, with only bony landmarks visible. A typical intracranial vascular anatomy was assumed.

Statistical analysis

All raw data were analyzed using a statistical software package of SPSS for Windows version 22.0 (SPSS, Inc., Chicago, IL). *The level of significance was calculated with a Mann–Whitney U test, the significance level was set at $\alpha = 0.05$.* Cohen's k-statistic was calculated to quantify the inter-observer and intra-observer reproducibility. A value of $1 \geq \kappa > 0.6$ was used to indicate a high level of reproducibility and $0.6 < \kappa < 0.4$ for moderate reproducibility. Multivariate logistic regression analysis was performed with vessel wall alterations (binary assessed) as dependent variable and with radiation dose and years after primary RCT as independent variables. Two models, one being VBC vessel wall changes and one being ICA vessel wall changes, were calculated. Presented are the odds ratios and the concerning p-values and 95% confidence limits. All analyses are explorative. For these analyses, a p-value of <0.05 was considered as statistically significant. No adjustments for multiple testing have been done here.

Results

Characteristics of the patients

Of the 66 former MB patients (mean age [in years] at diagnosis 7.5 ± 3.4, range 3–17, 30 female) who met the inclusion criteria, 22 (mean age [in years] at diagnosis 8.4 ± 3.4, range 4–17; mean age [in years] at MR scan 25.3 years ± 12.4, range 10–53, 17 female; mean years after primary RCT 16.3 ± 11.9 years, range 1–45) were eligible for MR examination. Vessel wall changes were observed in

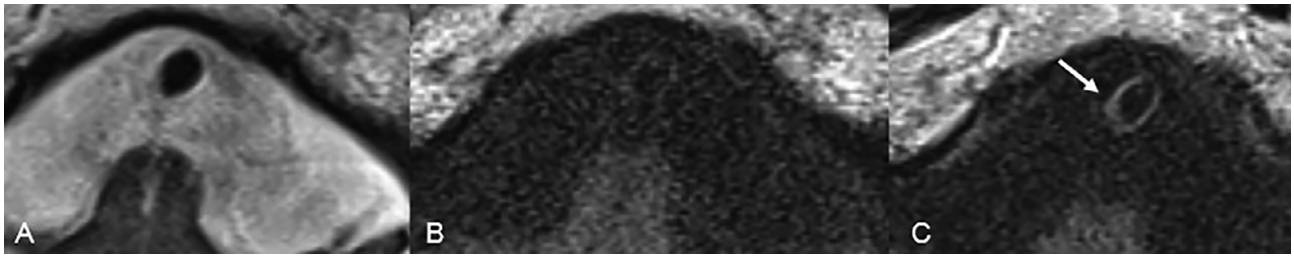

Fig. 2. (A) High resolution VWI T2 weighted, (B) high resolution VWI pre-contrast T1 weighted, (C) high resolution VWI post-contrast T1 weighted with concentric contrast enhancement and vessel wall thickening of the basilar artery (arrow).

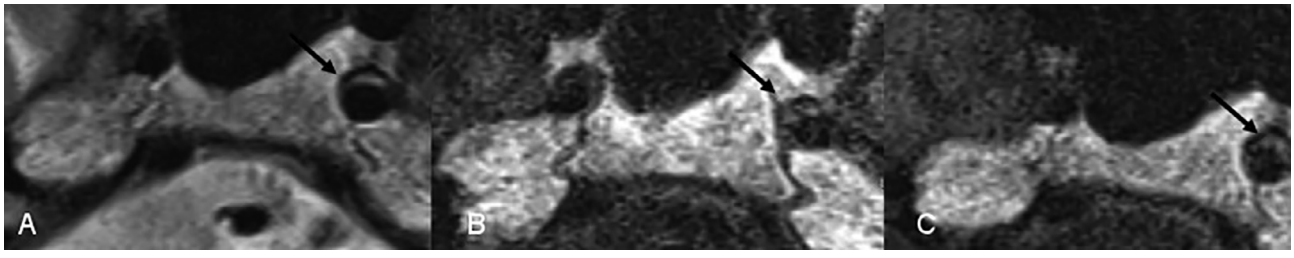

Fig. 3. (A) High resolution VWI T2 weighted, (B) high resolution VWI pre-contrast T1 weighted, (C) high resolution VWI post-contrast T1 weighted, all images reveal an eccentric vessel wall thickening of the left intracranial internal carotid artery (arrow).

Table 1
Analyzed characteristics for all patients, for patients with and without vessel wall changes.

Characteristics	All patients ($n = 22$)	Patients with vessel wall changes ($n = 14$)	Patients without vessel wall changes ($n = 8$)	p-Value
Age [years] at diagnose	8.4 ± 3.5 4–17	8.4 ± 2.1 6–13	8.5 ± 5.4 4–17	>0.05
Gender				
Female	17	10	7	>0.05
Age at MR scan [years]	25.3 ± 12.4 10–53	30.6 ± 12.5 10–53	15.9 ± 3.6* 10–20	<0.05
Duration after RCT [years]	16.6 ± 11.9 1–45	22.2 ± 11.2 6–45	6.9 ± 4.1* 1–14	<0.05
Prescribed dose to the whole brain [Gy]	30.1 ± 5.3 23.4–40	31.7 ± 4.6 23.4–40	27.2 ± 5.5 23.4–35.2	=0.05
Prescribed dose to the posterior fossa/tumor site [Gy]	54.5 ± 1.8 50.2–60	54.5 ± 2.3 50.2–60	54.5 ± 0.7 54–55.6	>0.05
Estimated dose to intracranial ICA [Gy]				
23.4–30.0	3	3	0	>0.05
30.1–40.0	9	7	2	
40.1–50.0	5	3	2	
>50	5	1	4	
Estimated dose to VBC [Gy]				
23.4–30.0	0	0	0	>0.05
30.1–40.0	2	2	0	
40.1–50.0	5	4	1	
>50	15	8	7	
Single dose craniospinal irradiation [Gy]				
1.5	3	3	0	>0.05
1.6	11	8	3	
1.8	7	2	5	
2	1	1	0	
Single dose posterior fossa [Gy]				
1.5	1	1	0	>0.05
1.8	4	2	2	
2	17	11	6	
BMI	23 ± 5.1 16.9–34.4	24.5 ± 5.6 16.9–34.4	20.5 ± 2.7 17.9–25.6	>0.05
Smoking habit	0	0	0	

* Significant ($p < 0.05$).

14 of the 22 patients (63.6%); 1 had vessel wall changes in the intracranial ICA only, 7 in the VBC and 6 in both (Figs. 1–3 and Table 1).

After binary assessment of the vessel wall alterations (present vs. not present), patients were divided into two subgroups, with vessel wall changes and without vessel wall changes. Descriptive data for the patients with and without vessel wall changes, including age at diagnosis, years after primary RCT, age at MR scan. The estimated whole brain radiation to the intracranial ICA and VBC was divided into subgroups and reported in Table 1. The radiation dose to the posterior fossa/tumor site (boost), the whole brain radiation fractionation and boost fractionation were reported in Table 1 as well. Furthermore, BMI and smoking habit are reported, showing not significant differences. Significant differences were observed for years post primary RCT and age at MR scan. Mean years after primary RCT for patients with vessel wall changes was 22.2 ± 11.2 (6–45) vs. 6.9 ± 4.1 (1–14) for patients without vessel wall changes (Table 1). A relevant difference ($p = 0.05$) was found for the prescribed dose to the whole brain with 31.7 GY for patients with vessel wall changes vs. 27.2 GY for those without vessel wall changes. Table 2 shows the distribution of the character of vessel wall (eccentric vs. circumferential vs. combined), with a majority of circumferential thickening for the VBC.

Table 2
Shows the distribution of the different character of vessel wall thickening for both ACIs and the VBC.

Character of the vessel wall thickening	ACI	VBC
Eccentric	3	3
Circumferential	1	7
Combined	2	2

To reduce possible statistical inaccuracies, intra- and inter-reader reliability tests were performed, showing a high consistency.

The intra-reader reliability for vessel wall changes in the post-contrast T1 sequences for qualitative vessel wall examination was reported high for the VBC and intracranial ICA with a $\kappa = 0.93 \pm 0.06$ and $\kappa = 0.82 \pm 0.11$. A high inter-reader reliability was reported for both, VBC and intracranial ICA, with a $\kappa = 0.93 \pm 0.06$ and $\kappa = 0.90 \pm 0.10$.

Results of the multivariate logistic regression analysis are shown in Table 3. Two models of a multivariate regression analyses were tested. One was tested for the ICA and one for the VBC, with VW changes as the dependent variable and "radiation dose" and "years post RCT" as covariates, respectively. The fit of the model was tested with Nagelkerke's R-squared with: 0.688 for the VBC with 0.526 for the ICA. Table 3 shows that the only covariate with a significant impact is years post RCT for the VBC, with $p < 0.05$ and with an odd's ratio = 1.38.

Discussion

For the last 50 years, the standard therapy of medulloblastoma patients involves the use of craniospinal irradiation (24–36 Gy) with boost to the posterior fossa/primary tumor bed (54–60 Gy) [3]. Even though doses and radiation fields have been minimized as far as possible, the damage to surrounding normal tissue and well-described late sequelae occurs [18], including cerebrovascular disease and stroke [19,20].

Table 3
Is showing the odds ratio (OR), the confidence interval (CI) and the *p*-values of a multivariate logistic regression models with radiation dose and years after primary RCT as independent variables. Two separate models, with a binary outcome (vessel wall changes vs. no vessel wall changes) were tested. One model, being VBC vessel wall changes and one model being ICA vessel wall changes were calculated.

	VBC			ACI		
Variables	OR	95% CI of OR	*p*-Value	OR	95% CI of OR	*p*-Value
Estimated radiation dose [Gy]	0.37	0.03–5.13	0.46	0.05	0.00–1.7	0.1
Duration after RCT [years]	1.38	1.04–1.84	0.03	1.34	0.9–1.99	0.15

Late sequelae gain more relevance as there has been an increase in overall survival of medulloblastoma patients over the past 20 years [3] due to improvements in treatment.

A report from the Childhood Cancer Survivors Study describes that the risk of late-occurring stroke in pediatric brain tumor survivors is, independently of radiation treatment, about 30-fold higher in comparison to healthy siblings. In case of previous treatment with radiation, it is almost 40-fold higher with a 25-year cumulative incidence of 6.9% [19]. Furthermore additional usage of alkylating agents like Cyclophosphamide and Lomustine (CCNU), commonly used in medulloblastoma therapy, seem to increase stroke risk even more [19].

According to the current literature late occurring strokes in cancer survivors are induced by radiation induced vessel wall abnormalities [21].

After radiation exposure, there is a release of a variety of proinflammatory substances, leading to an inflammatory process [22], resulting in vascular injury with several types of lesions (e.g. adventitial or per adventitial sclerosis) [10]. This contributes to morphological features similar to those seen in spontaneous atherosclerosis [23]. Carotid intima media thickness (CIMT) is a frequently used parameter to evaluate atherosclerosis in clinical practice. Ultrasound based studies in patients revealed an increase in CIMT already one year post radiation therapy [5,8,17].

To our best knowledge, until today, no study investigated in vivo premature ICAD lesions in survivors of childhood brain tumor, after RCT.

Therefore, this study assesses ICA lesions and lesions of the VBC through high resolution MRI. However, the analysis of the MR images could only be performed qualitatively and not Congruous with the current literature this study shows that increasing general age of former patients in irradiated childhood cancer survivors is related to an increased development of atherosclerotic vessel wall changes [5,24]. Similar results were found in studies with adult head and neck cancer patients for the extracranial ICA imaged through ultrasound [7,9]. These findings are emphasized by this study, reporting a significant difference in age at MR scan for the patients with vessel wall changes, with a mean age of 30.6 ± 12.5 years. However, in comparison to non-irradiated patients a mean age of 30.6 is very young for atherosclerotic vessel wall changes, as non-irradiated patients rarely show carotid artery disease before the age of 50 [7]. Thus, the latency between radiation therapy and the development of relevant occlusive stenosis and symptoms in the former pediatric medulloblastoma patients remains unknown [6].

The multivariate regression analysis report for the VBV, time after RCT, as the strongest independent predictor for developing vessel wall alterations (Table 3) for the VBC. Age at MR scan was not added as a covariate to the model. Given MB is a childhood tumor and the two parameters, "age at MR scan" and "years post RCT" are correlated (older patients will have higher values for years post RCT). In conclusion, a model including both covariates "age at MR scan" and "years post RCT" would be problematic due to correlation. Age at MR scan showed a significant difference between the patients with and without vessel wall changes in our study and if used as a covariate in a univariate regression model with vessel wall changes as a dependent variable, a significant impact would be found with a good fit of the model (Nagelkerke's R-squared = 0.503), thus an influence through higher age in developing intracranial vessel wall changes is plausible [5,24]. However the mean age of 30.6 years in this study is very young for atherosclerotic vessel wall changes and it is more likely that the patients in the underlying study show arteriosclerotic vessel wall changes due to the RCT.

Radiation dose is independent of both "age at MR scan" and "years post RCT" a model with both " radiation dose" and "age at MR scan" would not invalidate the predictive power of "radiation dose". However, we did not correct the odd's ratio for "age at MR scan". There are a number of exploratory variables that could be tested in further studies. The underlying study wanted to investigate the following: (a) if high resolution MR could be used as a tool to reveal vessel wall changes before they are clinically apparent, (b) how long is the duration after RCT when vessel wall changes are observed the first time and (c) if the different applied radiation doses have an impact on vessel wall changes. Therefor we focused on "years post RCT" and "radiation dose" as covariates.

In our opinion a standardized MR protocol for monitoring former childhood MB patients in regard to years post RCT would be helpful to gain comparable MR images in different institutes. Giving the possibility to monitor clinically non-apparent vessel damages and the progress of those, it might be possible to reduce the risk of further damages through e.g. stroke and hereby to improve the quality of life of the patients.

Different radiation dose protocols have been tested and applied over the years. Even though the underlying study could not show a significant impact of the applied radiation dose on vascular changes, in further studies with new, individualized radiation protocols, the effects on the vessels might be observed earlier and in an standardized manner and thus easily compared with each other.

With patients of this study intracranial vessel wall alterations were observed no earlier than six years after RCT. This is consistent with Bitzer and Topka, reporting radiation induced extracranial arteriopathy lesions between 4 months and 24 years following cervical or brain irradiation in former childhood cancer patients [25].

In relation to the applied radiation dose, animal studies [26] and human cancer studies have shown a relationship between radiation and vascular injury [5,27]. Human cancer studies in adult patients report an increased CIMT or rise of the arterial lesions with increasing doses of radiation to the neck, suggesting dose induced vessel wall changes [27]. Many studies suggest a relationship between radiation dose and the risk of stroke in pediatric patients treated by cranial radiotherapy [19,20].

A significant correlation between the estimated radiation dose to the intracranial ICA and VBC and vessel wall changes was not evidenced by this study. However, 20% of the patients with an estimated radiation dose, higher than 50 GY, to the ACI are showing vessel wall changes, in comparison to this, 53% of the patients with a similar dose show vessel wall changes for the VBC. A higher likelihood for VBC vessel wall changes with higher doses might be discussed. This hypothesis would be in line with the results from Haddy et al. [28]. They demonstrated, that the radiation dose applied to the prepontine cistern has a higher impact for the devel-

opment of cerebrovascular disease than a similar radiation dose to any other part of the brain [28]. The prepontine cistern includes parts of the VBC. Nevertheless, the binary regression analyses, with an odds ratio of 0.37 and a *p*-value of 0.46, shows no significant shows no significant correlation for dose depending vessel wall changes.

The inherent small vessel size of intracranial arteries and their tortuous course creates considerable difficulties for imaging. Therefore the MR imaging is the method of choice. Nevertheless, the small vessel size would ideally require an even higher in-plane resolution, allowing a comparable measurement to ultrasound CIMT examinations [13,29]. The in-plane resolution should be ideally <0.2 mm using an isotropic 3D technique at the best [13,29]. However, this technique standard is not available at the time.

A further limitation of this study is the relatively small patient cohort, the heterogeneous period of time after primary RCT and possible impreciseness of the estimated vessel doses.

In conclusion this study was able to show, that high resolution MRI is capable to detect intracranial vessel wall changes in pediatric medulloblastoma survivors, after RCT. Furthermore, we observed a significant correlation between years post RCT and the development of intracranial vessel wall changes in irradiated pediatric medulloblastoma survivors. Our findings and the findings in the literature [30] confirm, that monitoring late sequelae of RCT in the intracranial vessel walls during regular follow-up examinations is of interest. As proven by this study, high resolution MRI is an appropriate tool for imaging premature ICAD, which may be helpful in identifying patients at an increased risk for later ICAD-related complications requiring closer follow-up. Furthermore, investigations of premature ICAD after RCT may lead to an improvement of actual cranial radiation protocols, aiming to decrease late sequelae.

Competing interest statement

The authors declare that they have no competing interests.

Declaration of interest

None.

Conflict of interest

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors declare that they have no competing interests. Institutional Review Board approval was obtained. Written informed consent was obtained from all patients in this study.

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