Original Articles

Pediatric CNS imaging and long-term effects of irradiation in pediatric oncology patients

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Abstract   ***Background***: The aim of this study was to evaluate post-irradiation changes in the central nervous system (CNS) detected using magnetic resonance (MR) imaging.
Methods: Magnetic resonance images of 15 children with CNS tumors treated through whole-brain irradiation over 10 years were reviewed retrospectively. Variables such as age at the time of irradiation, total radiation dose, treatment length, and time interval between irradiation and MR changes, were evaluated.
Results: All patients included in the study had imaging abnormalities of the CNS. Eight patients (53%) developed CNS abnormalities within a short period of time – only a few months after irradiation (mean 4.8 months). Seven patients (47%) developed CNS abnormalities within a long time interval after treatment (mean 4.6 years). In almost all patients, a T2 increase in supra- and infratentorial white matter was observed. Follow-up examinations showed nine patients (60%) with cerebellar atrophy.
Conclusions: In this sample of pediatric patients who underwent whole-brain irradiation, the time receiving irradiation was not related to the severity of the MR changes. A correlation between the age of the child or the length of the radiotherapy and the extent of the changes could not be confirmed. However, we observed a trend towards stronger brain parenchymal degeneration with cystic changes in the younger age group of children in our sample. Older children who received irradiation seem to be more susceptible to vascular dysplasia with cavernous hemangiomas and microbleeding.

Key words   child, irradiation, MRI, oncology, pediatrics.

Primary brain tumors are the most common solid tumors in the pediatric population and account for approximately 20% of all pediatric cancers and for 53% of all central nervous system (CNS) tumors in the pediatric population.[1,2] Cranial radiation therapy (CRT) is an integral part of the treatment of patients with CNS and other intracranial tumors or disorders with CNS involvement, to maintain a high cure and low relapse rate.[3,4] With acute leukemia or primary brain tumors like glioma, ependymoma, medulloblastoma, pilocytic astrocytoma, neuroblastoma, and germ cell tumors, with primary CNS lymphoma, CRT is used to prevent a central nervous system relapse.[5,6] Surgical removal is the treatment of choice, followed by surveillance, radiotherapy, or chemotherapy.[1,7-9] As current therapeutic strategies achieve an excellent long-term survival rate, potential treatment-induced late effects are increasingly observed, which lead some authors to question the necessity

for radiotherapy, especially with younger children.[10] As the children's survival rate and duration increases, the focus has shifted to the long-term effects of the therapy. Several studies have shown that neuropsychological outcomes depend on age at treatment and dose of cranial radiotherapy, and that a reduction in CRT dose may limit the effects on intellectual function.[1]

Usually, cranial irradiation is only carried out on patients older than 4 years because of an increased risk of severe late effects with CRT for younger patients.[8] At 2–3 years of age the child's cortex has developed 90% of its later weight, neurogenesis and gliogenesis have mostly been completed, and synaptic density has reached its peak.[11] For patients under the age of 4 years, the standard method is chemotherapy.[12] In rare cases, for example if the tumor is inoperable, irradiation can also be considered for children younger than 4 years of age.

Recently, concerns about the late toxic effects that might arise from radiation therapy of the whole brain in young patients led to suggestions that reduced field radiation could be adequate for the cure as well.[6] Known late complications of whole-brain irradiation include a wide spectrum of

abnormalities ranging from subclinical changes that are only detectable by magnetic resonance imaging (MRI) to endocrine dysfunction, cognitive impairment or secondary neoplasm by effects on the microenvironment that allow for growth of pre-existing malignant cells.[13,14] Furthermore, the risk of developing cavernous hemangioma (CH) has already been described in several studies.[5,6,15-18] It appears that all changes are likely to result from complex alterations with at least four contributing factors including damage to vessel structures, deletion of progenitor cells and mature oligodendrocytes, deletion of neural stem cells in the hippocampus, cerebellum, and cortex, and generalized alterations of cytokine expression.[10]

Magnetic resonance imaging of the CNS is a sensitive method and the usual procedure to diagnose adverse effects of CRT in adults as well as in pediatric patients.[19]

The aim of this study was to determine the effects of CRT (whole brain irradiation) and the extent of cerebral changes after irradiation depending on age during irradiation.

Methods

This retrospective review was approved by the institutional review board. Patient data were obtained from the electronic medical records including MRI data sets from the departments of neuroradiology and radiotherapy.

Inclusion criteria: We performed a retrospective analysis of all pediatric patients at the Children's Hospital of the Goethe University Frankfurt with CNS tumors, who received a whole brain irradiation in the period from January 1, 2007 to January 1, 2017 and whose data were electronically stored at the University of Frankfurt. We retrospectively analyzed the brain volume irradiated by a cumulative dose of 52.4 Gy on average (range 35.2-100 Gy) in all MRI examinations available to us. All but two patients received an additional radiation boost in the localization of the tumor. The protocols of magnetic resonance imaging examinations in this context include standard contrast-enhanced and also susceptibility-weighted sequences. Exclusion criteria were lesions of the brain parenchyma (with the exception of the primary tumor) before therapy. In addition, patients undergoing brachytherapy, radiosurgery or partial brain irradiation were not included in this study. The medical records were reviewed with attention to the age at the time of radiation therapy, the time of onset of imaging changes, and both clinical and imaging long-term outcome. Variables were compared using the χ^2 test.

Results

Patients: A total of 15 children with brain tumors, who fulfilled these criteria and received postoperative whole-brain CRT, were included in this study. Of these, one patient with germinoma did not receive any surgical therapy before starting the irradiation – only radiochemotherapy was performed. All patients were treated with chemotherapy, too. The 15 patients consisted of 11 male and four female participants. Mean age at time of CRT was 10.5 years. By default, the retrospectively analyzed MRI images were taken quarterly during the first 2 years after irradiation. In cases of pathological changes, that observation period was extended. In one patient the time interval between the available MRI examinations was only 4 months.

Time interval to signal alterations: All of the 15 patients included in the study (100%) were found to have CNS abnormalities within the course of MRI examinations. In eight patients, the first CNS abnormalities were detected after only a few months (mean 4.8 months); the other seven patients showed the first changes after some years (mean 4.6 years). As shown in Table 1, it was not possible to establish a correlation between the age of the patient during irradiation and the exact time at which the changes were observed for the first time, except for cystic changes, which were only observed in two patients, who were under 6 years of age at the time of irradiation. However, these cystic changes were not detectable in all patients, who were younger than 6 years of age at the time of irradiation. Patients in whom signal changes in the MRI were observed at the earliest possible time (in the first MRI examination 3 months after irradiation) were 2 years, 9 years, and 12 years old at the time of irradiation. On the other hand, patients in whom the signal changes occurred at least 5 years after irradiation were 6 years, 14 years, and 16 years of age and thus these patients also had a very large age range (Table 1).

Radiation dose: There was no significant correlation between the time interval (from irradiation to the appearance of MRI signal changes) and the total radiation dose – see Table 1. The shortest time interval for a patient (age at irradiation: 6 years) with the highest radiation dose (100 Gy) was 1 year, whereas the two patients (5 and 13 years of age during irradiation) with the second highest total radiation dose of 77.4 Gy clearly differ in time intervals with 6 months and 2 years between their irradiation and first occurrence of signal changes (Table 1). The patient with the lowest radiation dose with its delay between irradiation and the first detection of post-therapeutic MRI changes of the cerebral parenchyma after an interval of 2 years was in the relative midfield compared to the delay until the first occurrence of cerebral changes in the remaining patients. (Table 1).

All patients had numerous examinations over many years between the first post-radiogenic examination and the last examination available to us. Depending on the time interval between the follow-up examinations and the period of time since the detection of the disease, we had very different numbers and total intervals of all available follow-up examinations, whereby the total interval of the MRI examinations of each patient available to us included a minimum of 4 months and a maximum of 14 years. The median of the time intervals between onset of disease and last examination was 7.1 years. Post-radiation changes include a wide spectrum of signal abnormalities.

MRI anomalies: Considering the various parenchymal changes, 11 out of 15 patients were found to have changes of white matter with areas of increased signal intensity on T2-weighted sequences (Table 2). With eight out of these 11

Table 1 Patient data (age, diagnosis and therapy) as well as an exact list of MRI changes of the brain parenchyma at the respective examination times (time period since irradiation) and the time interval of all MRI examinations available to us

Diagnosis	Surgery (yes 1, no 0)	Radiation dose	Age at radiatio (years)	Chemotherapy (CTX)	Period from radiation to first MRI (months)	Signal 1. MRI	Period until first changes in MRI (months)	MRI with first signal changes	Period until last MRI (months)	Signal changes in last (in study included) MRI	Cysts	Time between MRI exam.	Symptoms
Medulloblastoma	1	23,4 Gy axis + 54 Gy infratent	16	1	1	Normal	159	Glioma lateral ventricula	60	Normal signal, cerebellar atrophy	0	14 y	Frontal lobe disorder, epilepsy
Medulloblastoma	1	36 Gy axis + Boost infratent 14 Gy	6	1	1	Normal	65	T2-increase infratentorially + pontin	124	Increasing T2 cerebellar + pontin, no atrophy	0	11 y	Slight palsy leg, insufficiency thyroid and pituitary gland, hearing loss
Medulloblastoma	1	40 Gy + Boost infratent 10 Gy	8	1	1	Normal	19	Increasing cm enhancement of op margins	60	cm enhancement op margins, cavernoma cerebellar r	0	5 y	
Medulloblastoma	1	23,4 GY axis + 30,6 infratent	12	1	1	Normal	1	T2-increase posterior brainstem, cerebellar atrophy	103	Global T2-increase, cm enhancement leptomeningeal	0	9 y	Cerebellar ataxia, intention-tremor, abducens paresis
Germinoma	0	23,4 Gy axis + 16,2 infratent	21	1	2	Normal	9	T2-increase colliculus inferior	116	T2-increase colliculus inferior	0	9 y	Insufficiency pituitary gland
Pilocytic astrocytoma	1	23,4 Gy + infratent 30,6 Gy	14	1	1	Normal	86	T2-increase Ncl. dentatus	134	Increasing T2-tumors, meningeosis carcinomatosa since 2013	0	11 y	MOTOR disabilities
Medulloblastoma	1	23,4 Gy + 54 Gy intratent	13	1	5	Normal	5	T2-increase deep white matter	48	T2-increase deep white matter and infratent, atrophy	0	4 y	Diplopia
Medulloblastoma	1	35,2 Gy axis	5	1	2	Normal	21	T2* signal loss = microbleeding	40	T2-increase infratent, atrophy	0	3 y	
Medulloblastoma	1	23,4 Gy axis + Boost infratent 54 Gy	5	1	1	Normal	22	Cerebellar T2-increase, atrophy	76	Atrophy	0	6 y	
Medulloblastoma	1	23,4 Gy axis + 30,6 Gy infratent	14	1	1	Cerebellar T2-increase, atrophy	9	T2* signal loss, atrophy	25	T2* signal loss, atrophy	0	2 y	Motor disabilities
Medulloblastoma	1	40 Gy axis	9	1	1	Normal	3	Slight T2-increase cerebellar and beginning Atrophy	4	Slight T2-increase cerebellar, atrophy	0	4 months	Ataxia
Medulloblastoma	1	23,4 Gy axis + 30,6 Gy infratent	13	1	1	Normal	5	Cerebellar T2-increase, atrophy	54	T2* signal loss, infratentorial T2-increase, atrophy	0	6 y	
Atypical teratoid/rhabdoid tumor	1	35,2 Gy axis + 19,8 Gy RoI	2	1	1	T2-increase supratentorial	2	Reduced T2-increase supratentorial	70	T2-increase supra- and infratentorial	1	6 y	
Medulloblastoma	1	23,4 Gy axis + 30,6 Gy infratent	14	1	1	Normal	31	Atrophy	105	T2* signal loss, infratentorial T2-increase, atrophy	0	9 y	
Medulloblastoma	1	40 Gy axis + 60 Gy infratent	6	1	3	Normal	18	T2-increase Ncl. dentatus	140	T2-increase cerebellar, atrophy	1	11 y	

patients, T2-hyperintensity was observed in the posterior fossa. In nine of 15 patients focal atrophy of the cerebral parenchyma was observed within the irradiated volume (Table 2). Contrast enhancement was evident with three of the 15 patients, which in two cases corresponded to postoperative granulation tissue and in one case to a meningeosis carcinomatosa. The reactive enhancement decreased in one case after an interval of 6 months, while in the other case no dynamic of the enhancement was observed over a period of 2 years. With 2 patients, suspected relapse was observed during the MRI examinations. In the patient with meningeosis carcinomatosa, the changes were detected 9 years after irradiation for the first time. In the other case, 14 years after irradiation a glioma was detected.[20] Cavernomas were observed in four patients. All our included patients underwent chemotherapy. A correlation between the chemotherapy and the changes therefore cannot be assessed. The same applies to surgery: with the exception of one patient, all patients underwent surgery. Although no atrophy was found here, five patients under surgery also showed no atrophy during the period of investigation.

Discussion

Although radiotherapy is an integral part of the treatment of various forms of malignant diseases, possible delayed effects due to treatment are still alarming. However, actual data providing findings of risks are scarce, especially with respect to whole-brain irradiation. Computed tomography (CT) scans were used for monitoring purposes before the widespread availability of MRI equipment. Nowadays monitoring is usually carried out using MRI. O Robin *et al.* described necrotizing changes in the brain parenchyma detected by CT as early as 1984 as a result of combined leukemia treatment of children with various drugs and radiation.[21]

Few existing studies investigating the therapeutic consequences of childhood brain tumors focus predominantly on volumetric measurements of the brain parenchyma or volume changes of specific brain regions. These frequently observed volume reductions of the hippocampus or white matter are associated with a memory dysfunction or decreased attentional abilities. According to Palmer *et al.,* the extent of the volume reductions could be associated with the irradiation dose.[22-25]

Table 2 A quantitative listing of the respective deleted MRI changes of the brain parenchyma and the corresponding percentage listing

MRI assessment of volume taken to full-dose of median 52.43 Gy (range 35.2-100 Gy) in 16 CNS tumor patients	
Variable	*n* (%)
Atrophy	9 (60)
T2-increase	11 (73)
Contrast enhancement	3 (20)
Malignancy (brain tumor, metastatic spread)	2 (13)
Cavernoma (signal loss in T2*)	4 (26)
Cystic changes	2 (13)

Steen *et al.* investigated T1 effects on gray and white matter by ionizing radiation in conformal radiation therapy and found that T1 mapping may be sensitive to radiation-related changes in human brain tissue.[26]

Therapy-related changes differ from normal brain changes. They display different signal strength, different content, and a different binding of hydrogen atoms, so they are easily recognizable with a T2 sequence.[27,28]

Among 134 patients in a study by Folulardi et al. with medulloblastoma or supratentorial primitive neuroectodermal tumor (PNET) treated prospectively with risk-adjusted craniospinal irradiation and conformal boost to the tumor bed, followed by four high-dose chemotherapy cycles with stem-cell rescue, 22 developed white matter lesions (WMLs) on T1-weighted imaging with and without contrast and/or T2-weighted imaging at a median of 7.8 months after starting therapy. Lesions were predominantly in the pons and cerebellum. Sixteen patients had WML resolution at a median of 6.2 months after onset; two patients developed necrosis and atrophy.[27]

Early therapy-induced changes occurred from 3 weeks to a few months after irradiation and were characterized by T2 hyperintensity of the white matter, usually without increases over time. These changes may have been due to demyelination or edema.[27-29] However, these are often not clearly defined. Johannesen *et al.* showed that late radiation-induced changes, as signal changes with or without enhancement, necrosis, and mass effects in T1 and T2, appear from several months to years after irradiation.[19] Regarding our study, circa 50% of the patients had early therapy-induced changes only few months after CRT, whereas the first MRI changes were observed in the other 50% only after several years. It should be kept in mind, that the first MRI examination after irradiation usually took place after 2 and 6 months, so early, temporary changes in some cases might be missed by the lack of an earlier examination. The T2-signal changes in the posterior fossa frequently observed in our study can be explained by the irradiation boost of the tumor target region in addition to whole brain irradiation in medulloblastomas, which are usually located infratentorally. Although not specifically measured in our study, some of the patients with cerebellar T2-signal changes had worse motor functions than in previous studies, for example by Ciesielski *et al.*[30]

As previously reported by several authors,[5,31,32] radiation-induced cavernous hemangiomas were found in almost one third of the long-term survivors in our study group. The four patients with signal reduction, a sign of micro-bleeding, were rather older. It is noticeable that the change only becomes apparent for some time after irradiation.

Several authors reported a link between age at CRT and the severity of parenchymal changes,[9,19,33] a presumption we could not substantiate in our investigation. This could be explained by the small sample of patients less than 6 years of age who underwent whole brain irradiation. However, in our study group, cystic changes were only observed in two very young patients (under 6 years of age). Furthermore, the youngest patient showed very early signal changes at the first

MRI examination, which could be an indirect sign of more significant changes.

Several authors have previously described a positive correlation between the dose rate and the extent of parenchymal changes.[6,10,19,29,34] In our study group, no significant correlation was observed between the dose and the extent of parenchymal changes, probably due to the limited number of patients.

Evidence of leukoencephalopathy has also been reported with patients receiving chemotherapy only, which makes it difficult to isolate the changes caused by irradiation or chemotherapy only or a combination of both.[10,29] All of the patients underwent chemotherapy. Additionally, in most cases the primary tumor site is the posterior fossa, where the cerebellum has been subjected to primary tumor-related compression, surgical intervention, and full-dose radiation therapy.

Whole-brain radiation therapy is still very rare in pediatric patients[35-38] and information on this is scarce. In particular there are hardly any studies on post-radiogenic changes in children under 5 years of age. Kitajima et al., however, describe an increased occurrence of cystic changes in very young patients after irradiation. In our study, children who were less than 5 years old, as to be expected, were underrepresented; a link between the age at the time of radiotherapy and the specific parenchymal changes could therefore not be confirmed.

A correlation between the age of the child or the length of the radiotherapy and the extent of the changes could not be confirmed in our sample. However, the only two patients who
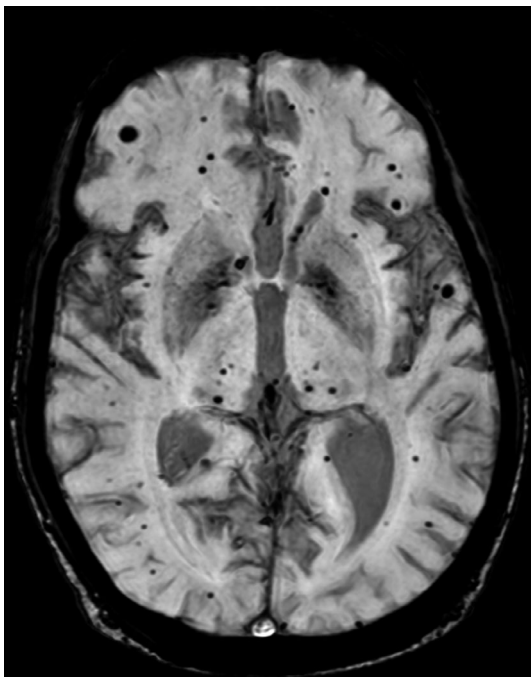

Fig. 2 Several cystic lesions in the white matter with an accent on the periventricular regions. In addition, there are moderately pronounced areal T2 signal increases in the white matter.

had cystic changes were under 6 years of age at the time of irradiation. The youngest patient at the time of irradiation also showed very early signal changes during its first MRI examination. It can be said that there was a trend to more severe brain parenchyma degeneration with cystic changes in the younger age group of children. Older patients are probably more prone to undergo vascular dysplasia with higher incidence of cavernous hemangiomas and micro-bleeding in this

Fig. 1 Gradient Echo T2* Weighted Imaging with numerous punctiform microbleedings on both sides ubiquitously distributed in the medullary bed, subcortical, but also in the deep gray matter.
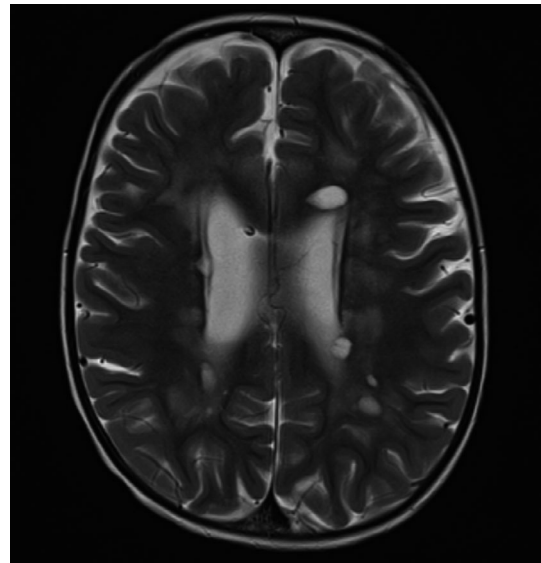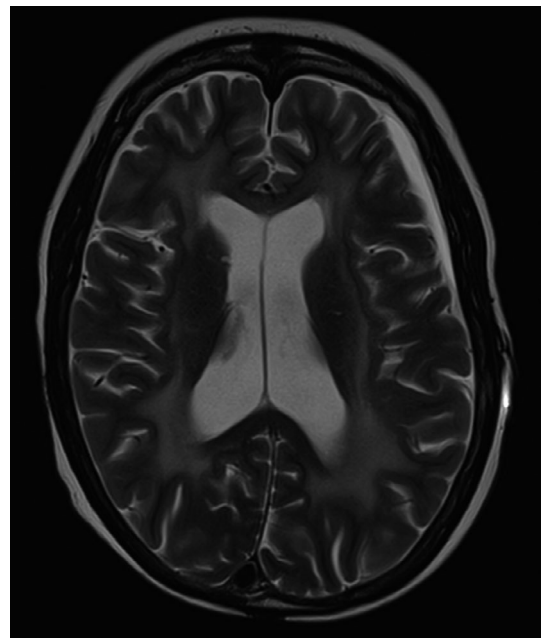

Fig. 3 In addition to a significant reduction in the volume of the white matter, there are pronounced confluent T2 signal increases in the white matter.

group. Due to the small sample size of children treated with whole-brain irradiation in individual institutions, further studies are needed to confirm this trend (Figs 1–3).

Disclosure

The authors declare no conflict of interest.

Author contributions

All data generated or analyzed during this study are included in this published article. L.P. contributed to the conception and design of this study. S.K. performed the statistical analysis and drafted the manuscript. T.L. and P.B. critically reviewed the manuscript and supervised the whole study process. All authors read and approved the final manuscript.

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