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V. Strenger[1] · H. Lackner[1] · R. Mayer[2] · P. Sminia[3] · P. Sovinz[1] · M. Mokry[4] · A. Pilhatsch[5] · M. Benesch[1] · W. Schwinger[1] · M. Seidel[1] · D. Sperl[1] · S. Schmidt[1] · C. Urban[1]

[1] Division of Pediatric Hematology/Oncology, Medical University of Graz
[2] Department of Radiotherapy, EBG MedAustron GmbH, Wiener Neustadt
[3] Department of Radiation Oncology, VU University Medical Center, Amsterdam
[4] Department of Neurosurgery, Medical University of Graz
[5] Division of Pediatric Radiology, Medical University of Graz

Incidence and clinical course of radionecrosis in children with brain tumors

A 20-year longitudinal observational study

Radiation therapy (RT) is a mainstay in the treatment of tumors of the central nervous system (CNS). Besides its unquestionable positive impact on survival, it is associated with a wide range of acute and late side effects [2, 6, 17]. Cerebral radionecrosis (RN) after treatment of brain tumors represents a severe and potentially devastating long-term complication that may be associated with considerable morbidity and even mortality [24]. The incidence of RN in patients treated for primary brain tumors is poorly defined. Studies in adults report incidence rates ranging from 3 up to 24% [7, 24]. The severity of symptoms due to focal necrosis is not only based on the size, but also on the location of the injury. If the necrotic volume is small and does not include regions like the motor cortex or the brain stem, this damage might go unobserved and remain clinically asymptomatic. On the other hand, the same-sized volume of necrosis located in one of the aforementioned sensitive regions can lead to significant morbidity. For details on histopathological and pathophysiological characteristics of brain necrosis we would refer to Barani et al. [4].

Clinically, the appearance of new lesions after treatment of brain tumors still poses a significant diagnostic challenge, since magnetic resonance imaging (MRI) cannot clearly distinguish between tumor recurrence and RN [16, 23]. Even second malignant neoplasms have to be taken into account. The importance of functional imaging, including FDG positron-emission tomography (FDG-PET) and MR spectroscopy, for discrimination between tumor progression and pseudoprogression remains to be discussed [7, 8, 16, 23]. The total RT dose and subsequent use of chemotherapy seem to be the most important risk factors for the development of RN in adults [24]. In adults, the clinical course of RN is variable, ranging from asymptomatic lesions with spontaneous recovery to rapid progression with development of neurological deterioration [7]. Little is known about the incidence and clinical course of RN in children treated for brain tumors. A spectrum of clinical syndromes after cancer treatment directed to the CNS in childhood has been described and includes radionecrosis, necrotizing leukoencephalopathy, mineralizing microangiopathy, cavernous hemangioma and secondary brain tumors [22, 27]. Asymptomatic MRI-detected changes have been reported in children treated for various brain tumors [3, 12, 13, 21]. Fouladi et al. [13] reported on asymptomatic and transient white matter lesions in 22 out of 134 children with medulloblastoma or primitive neuroectodermal tumor, two of whom developed RN. The aim of this retrospective, observational study was to describe a single-center's experience with RN in children treated for brain tumors over a period of 20 years.

Patients and methods

Study population

Between 1 January 1992 and 1 April 2012, a total of 107 consecutive children (62 male and 45 female, median age 9.4 years) underwent external photon beam RT for various brain tumors at the Dept. of Therapeutic Radiology and Oncology of the Medical University Graz. Patients additionally treated with gamma knife and/or reirradiation for relapse or progression were excluded from the analysis. Chemotherapeutic treatment and follow-up examinations were performed at the Dept. of Pediatric Hematology/Oncology Graz. The underlying diseases suffered by the

V. Strenger and H. Lackner contributed equally to this work.

Tab. 1 Patient characteristics and clinical course of 5 patients with RN following radiotherapy for malignant brain tumors

Patient	Gender	Age at RT (years)	Underlying disease (location)	RT	Total dose (Gy)	Fraction size (Gy), (no. of fractions)	EQD2 (Gy)	Chemotherapy	Diagnosis of RN (location)	Symptoms of RN	Interval between RT and RN (months)	Therapy for RN	Follow up (years)	Current symptoms
1	Female	5.4	Medulloblastoma (pons)	Craniospinal	35.2 Gy spinal 55.2 Gy cranial	1.6 Gy (×22) +2 Gy (×10)	31.7 Gy **51.7 Gy**	HIT 91	MRI, PET (pons)	Ataxia	105	No	18	Persistent neurological deficit
2	Male	6.9	Pilocytic astrocytoma (hypothalamic region) progression	Cranial	54 Gy	1.8 Gy (×30)	**51.3 Gy**	LGG study	MRI (fronto-parietal)	Cephalea	131	DXM	16	No
3	Male	7.7	Medulloblastoma (pons)	Craniospinal	35.2 Gy spinal 55.2 Gy cranial	1.6 Gy (×22) +2 Gy (×10)	31.7 Gy **51.7 Gy**	HIT 91	MRI, PET (cerebellum)	Severe ataxia	9	DXM	11	No
4	Male	5.2	Ependymoma (frontal left) relapse (2×)	Cranial	68 Gy	1 Gy/twice daily (×68)	**51 Gy**	HIT 2000, VCR, CY, CARBO, ETO, CCNU, CIS, MTX, ARA-C, THAL	MRI, histology (frontal left)	None	11	Resection (histology: RN)	3	No
5	Male	14.5	Osteosarcoma brain metastasis (temporal right)	Cranial	60 Gy	2 Gy (×30)	**60 Gy**	COSS 96, IFN, ATRA	MRI, PET, MR spectroscopy (cerebellum, mesenchephalon, mesiotemporal right)	Ataxia hemiparesis facial paralysis	5	DXM,HBO, bevacizu-mab	6	Persistent neurological deficit

MRI magnetic resonance imaging, *PET* positron-emission tomography, *DXM* dexamethasone, *RN* radionecrosis, *RT* radiotherapy, *HBO* hyperbaric oxygen, *VCR* vincristine, *CY* cyclophosphamide, *CARBO* carboplatin, *ETO* etoposide, *CCNU* lomustine, *THAL* thalidomide, *ATRA* vesanoid, *IFN* interferon gamma, *ARA-C* cytarabine, *EQD2* biologically equivalent total dose to nervous tissue when applied in 2 Gy fractions. Total radiation doses (Gy) to the cranium are in *boldface*.

patients were primitive neuroectodermal tumor (PNET)/medulloblastoma (n=32), PNET (supratentorial) (n=13), ependymoma (n=10), pontine glioma (n=14), astrocytoma (n=16), glioblastoma (n=5), craniopharyngeoma (n=3), intracranial germ cell tumor (n=10) and others (n=4). Patients were treated with adjuvant chemotherapy according to the international study protocols HIT 91, HIT 2000, HIT LGG 1996, MAKEI 89, SIOP-CNS-GCT-96 and COSS-96, or with temozolomide monotherapy [5, 9, 15, 28]. Median follow-up duration is currently 4.6 years (range 0.29–20.1 years). Suspicion of RN arose if MRI revealed new lesions in cases where signs of RN were already evident, as previously described [7, 16, 23]. Suspicions were subsequently confirmed by biopsy (n=1) or substantiated by FDG-PET or MR spectroscopy. In all cases of RN included in this study, relapse or progression of the underlying disease was ruled out by resolution of the lesions during follow-up.

Analysis of EQD2

Over the decades, patients were treated according to different study protocols, with irradiation treatment schemes that differed in terms of total dose, fraction dose and the number of fractions. To facilitate comparison of data from the different studies, the tolerance dose of normal brain tissue is presented as the biologically equivalent total dose as applied in 2 Gy fractions (EQD2), as opposed to the "physical" dose. The EQD2 values were calculated according to the linear-quadratic (LQ) formula. An α/β ratio of 2 Gy was selected for the late response of normal nervous tissue as previously described [20]. The LQ model is generally accepted for dose-fractionation analyses in clinical RT [4, 14, 25].

The study was approved by the ethics committee of the Medical University of Graz.

Results

Out of 107 patients treated with external brain irradiation during the analyzed period, 5 (4.7%) developed RN (**Tab. 1**). Prior to development of RN, all 5 patients had received cytotoxic chemother-

Abstract · Zusammenfassung

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Incidence and clinical course of radionecrosis in children with brain tumors. A 20-year longitudinal observational study

Abstract

Radionecrosis (RN) in children treated for brain tumors represents a potentially severe long-term complication. Its diagnosis is challenging, since magnetic resonance imaging (MRI) cannot clearly discriminate between RN and tumor recurrence. A retrospective single-center study was undertaken to describe the incidence and clinical course of RN in a cohort of 107 children treated with external radiotherapy (RT) for various brain tumors between 1992 and 2012. During a median follow-up of 4.6 years (range 0.29–20.1 years), RN was implied by suspicious MRI findings in in 5 children (4.7%), 5–131 months after RT. Suspicion was confirmed histologically (1 patient) or substantiated by FDG positron-emission tomography (FDG-PET, 2 patients) or by FDG-PET and MR spectroscopy (1 patient). Before developing RN, all 5 patients had received cytotoxic chemotherapy in addition to RT. In addition to standard treatment protocols, 2 patients had received further chemotherapy for progression or relapse. Median radiation dose expressed as the biologically equivalent total dose applied in 2 Gy fractions (EQD2) was 51.7 Gy (range 51.0–60.0 Gy). At RN onset, 4 children presented with neurological symptoms. Treatment of RN included resection (n=1), corticosteroids (n=2) and a combination of corticosteroids, hyperbaric oxygen (HBO) and bevacizumab (n=1). One patient with asymptomatic RN was not treated. Complete radiological regression of the lesions was observed in all patients. Clinical symptoms normalized in 3 patients, whereas 2 developed permanent severe neurological deficits. RN represents a severe long-term treatment complication in children with brain tumors. The spectrum of clinical presentation is wide; ranging from asymptomatic lesions to progressive neurological deterioration. FDG-PET and MR spectroscopy may be useful for distinguishing between RN and tumor recurrence. Treatment options in patients with symptomatic RN include conservative management (steroids, HBO, bevacizumab) and surgical resection.

Keywords

Paediatric oncology · Radiotherapy · Chemotherapy · Late effects · Cerebral radionecrosis

Inzidenz und klinischer Verlauf von Radionekrosen bei Kindern mit Schädeltumoren. Eine 20-Jahres-Langzeit-Beobachtungsstudie

Zusammenfassung

Radionekrosen (RN) bei Kindern nach Behandlung von Schädeltumoren stellen eine schwerwiegende Komplikation mit teilweise lebenslangen Spätfolgen dar. Die Unterscheidung zwischen RN und Tumorrezidiv oder -progression ist mittels Magnetresonanztomographie (MRT) nicht immer eindeutig möglich. In einer retrospektiven Single-Center-Studie beschreiben wir Inzidenz und klinischen Verlauf der RN. Bei 5 (4,7%) von 107 Kindern, die in den Jahren 1992 bis 2012 wegen unterschiedlicher Schädeltumoren eine Strahlentherapie erhalten hatten, erhärtete sich während des medianen Nachbeobachtungszeitraums von 4,6 (0,29–20,1) Jahren 5–131 Monate nach Bestrahlung der Verdacht auf eine RN. Dieser wurde entweder histologisch (1 Patient) oder mittels FDG-Positronenemissionstomographie (FDG-PET; 2 Patienten) oder mittels MR-Spektroskopie und FDG-PET (1 Patient) bestätigt. Alle 5 Patienten waren vor Auftreten der RN mit einer zytotoxischen Chemotherapie behandelt worden. Wegen Relaps bzw. Progression wurden bei 2 Patienten weitere Chemotherapeutika – zusätzlich zum jeweiligen Standardtherapieprotokoll – verabreicht. Die mediane Strahlendosis, ausgedrückt als Bioequivalenzdosis EQD2, betrug 51,7 Gy (51,0–60,0 Gy). Neurologische Symptome beim Auftreten der RN zeigten 4 Kinder. Die Behandlung bestand aus Resektion (n=1), Kortikosteroiden (n=2) oder einer Kombination aus Kortikosteroiden, hyperbarer Oxigenierung und Bevacizumab (n=1). Ein asymptomatischer Patienten erhielt keine Therapie. Bei allen Patienten kam es zu einer kompletten radiologischen Rückbildung der Läsionen. Bei 3 Patienten reduzierte sich die Symptomatik; 2 Patienten leiden weiterhin an schweren neurologischen Defiziten. RN stellen eine schwerwiegende Langzeitkomplikation bei Kindern nach Behandlung eines Schädeltumors dar. Die Bandbreite der klinischen Symptomatik reicht von asymptomatischen Läsionen bis hin zu fortschreitender neurologischer Symptomatik. FDG-PET und MR-Spektroskopie helfen, RN von Tumorrezidiv oder -progression zu unterscheiden. Die Behandlungsmöglichkeiten bei symptomatischen Patienten umfassen konservatives Management (Kortikosteroide, hyperbare Oxygenierung, Bevacizumab) sowie die chirurgische Resektion.

Schlüsselwörter

Pädiatrische Onkologie · Strahlentherapie · Chemotherapie · Spätkomplikation · Zerebrale Radionekrose

apy in addition to RT. An anthracycline containing protocol (COSS 96 with a cumulative doxorubicin dosage of 450 mg/m^2) was administered in patient number 5. In addition to standard treatment protocols, 2 patients had received chemotherapy for progression or relapse. Median irradiation doses to the brain expressed in EQD2 values were similar in the 5 patients with signs of RN (median 51.7 Gy, range 51.0–60.0 Gy) and the 102 patients who did not show signs of RN (median 51.3 Gy, range 50.0–60.0 Gy. In those patients with RN, the median age at irradiation was 6.9 years (range 5.2–15.4 years); the underlying diagnoses were astrocytoma (n=1), medulloblastoma (n=2), ependymoma (n=1) and brain metastasis of osteosarcoma (n=1). The median interval between irradiation and the onset of RN was 11 months (range 5–131 months). Four of the 5 patients developed neurological symptoms before diagnosis of RN. MRI showed suspicious new lesions in

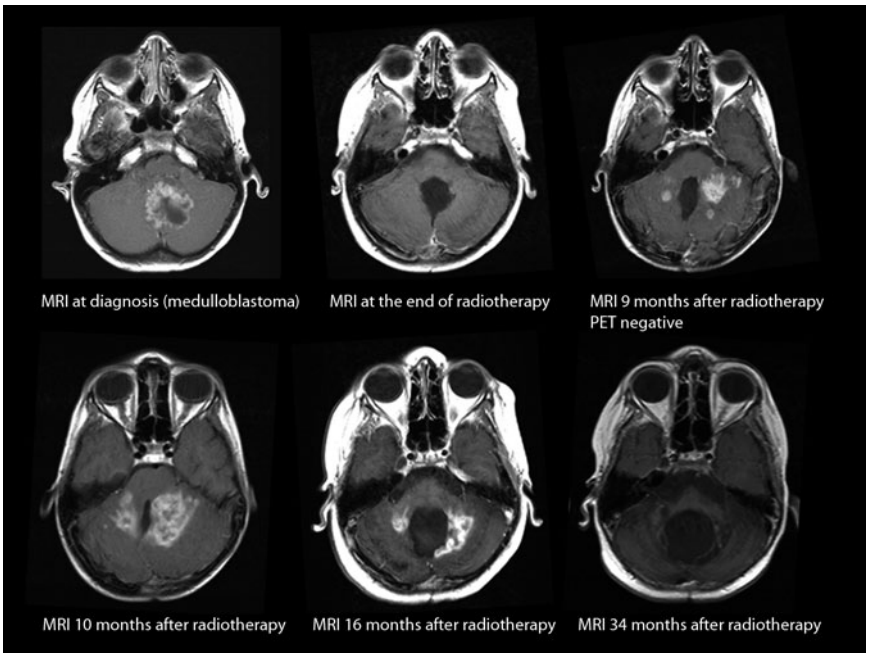

Fig. 1 ▲ Magnetic resonance imaging (MRI) of patient 3 at diagnosis, after radiotherapy and during follow-up. *PET* positron-emission tomography

all patients. In 3 out of 5 patients, subsequently performed FDG-PET showed decreased FDG uptake and in one of these patients, additional MR spectroscopy showed decreased levels of choline. Decreased FDG uptake and decreased choline levels are both indicative of RN. In 1 patient with unclear lesions highly suspicious for tumor recurrence, the new lesion was resected and a histological diagnosis of RN was made. Treatment of RN included complete resection in 1 patient, dexamethasone in 2 patients and a combination of dexamethasone, bevacizumab and hyperbaric oxygen (HBO) therapy in 1 patient [1, 11, 18]. One patient with asymptomatic lesions received no specific treatment. MRI lesions resolved in all patients (◘ **Fig. 1**), although 2 patients (numbers 3 and 5) still require intensive physical rehabilitation due to severe persistent neurological deficits.

Discussion

There is little known about the incidence of RN in children treated for brain tumors. Among adult patients, the reported incidence rates range from 3 to 24% [7, 24]. Ruben et al. [24] reported a 4.9% incidence of RN in a series of 426 adult patients treated for glioma, with a mean interval between RT and the onset of RN of 11.6 months. These data are comparable to those of our study, where RN was documented in 4.67% of 107 children, after a median interval of 11 months following external photon beam RT. Known risk factors for the development of RN are the total RT dose delivered and the subsequent application of chemotherapy [7, 24]. In our group of pediatric patients, no significant difference in the applied dose calculated as EQD2 was found, possibly due to the small size of the cohort. The EQD2 biological dose estimation permits comparison of different RT schemes [20, 26].

Chemotherapy in addition to RT might support the development of RN [24]. In our series, chemotherapeutic treatment for relapse or progression was given after initial radiochemotherapy in two patients. One patient had received an anthracycline containing protocol as the initial treatment. The spectrum of clinical manifestations of RN is extremely wide, ranging from asymptomatic lesions to spontaneous recovery and progressive neurological deficits that may be irreversible, and sometimes even cause death [23, 24]. Some authors have provocatively postulated that survival of patients with glioblastoma may be more favorable after the development of RN [7, 24]. In our study, one of the 5 patients with RN suffered no symptoms. The other 4 patients presented with neurological symptoms and in two of these cases, the patients developed persistent deficits despite multimodal therapy. Diagnosis of RN and discrimination between tumor progression and pseudoprogression is still a challenging issue [7, 8]. MRI-based RN findings are often nonspecific and frequently indistinguishable from tumor recurrence [23]. The lesions are described as a ring-enhancing mass with variable edema and mass effect [23], or lesions with a soap bubble or Swiss cheese pattern [16] closely mimicking the pattern of recurrent brain tumor. In lesions highly suspicious for tumor recurrence, biopsy still remains the diagnostic gold standard; however, its use is limited by its invasive nature and the potential heterogeneity of the lesions. Functional imaging, including FDG-PET or MR spectroscopy is considered increasingly useful for differentiating RN from tumor recurrence [7, 10, 16, 23]. FDG-PET in patients with RN usually shows decreased uptake of radionuclide in relation to normal brain tissue [7, 10, 23]. MR spectroscopy demonstrates low levels of choline in RN and high levels of choline in the presence of tumor progression [7, 23]. In our series, diagnosis of RN was established histologically in 1 patient, suspicion of RN was substantiated by FDG-PET showing decreased uptake of radionuclide in 3 patients and MR spectroscopy showed decreased levels of choline in one of the patients who was also examined by PDG-PET. However, we also have experience of a 12-year-old girl with PNET who developed neurological deterioration after radiochemotherapy. MRI showed lesions suspicious for RN, and FDG-PET was negative. The neurological symptoms in this patient progressively increased, leading to death despite treatment for RN including steroids, bevacizumab and HBO. Autopsy revealed recurrent disease. Therefore, it must be stated that functional imaging is always associated with a residual risk of misdiagnosis.

Regarding the dose–response relationship, the risk of RN was reported to increase with increased total dose and dose per fraction, as well as with increasing tissue volume [4]. In a review by Brands-

ma et al. based on several clinical studies of childhood brain tumors, a threshold EQD2 value of approximately 45 Gy was estimated for the development of RN, with a steep increase in the risk of RN above 60 Gy. Our data show an incidence of 4.7% following EQD2 doses in the range of 50–60 Gy and thus agree with this analysis. The latency period associated with RN is highly variable, with a minimum latency of about 3 months after radiation exposure [4]. The pathophysiology of RN is not completely understood. Kumar et al. [16] postulate mechanisms including vascular injury, glial and white matter damage, effects on the fibrinolytic enzyme system and immune mechanisms. Management of patients with RN is variable and depends on the clinical presentation. In patients with asymptomatic lesions, a wait-and-see strategy seems to be justified. In patients with neurological symptoms, several conservative treatment options are advocated, including corticosteroids, HBO and more recently, bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF) [1, 7, 11, 18]. The rationale for the use of HBO is the hypothesis that it might increase the partial pressure of oxygen (pO_2) in the tissue and thus enhance angiogenesis [1, 7, 11, 19]. The use of bevacizumab is based on the current hypothesis that RN might result from endothelial dysfunction leading to tissue hypoxia with concomitant liberation of VEGF. Levin et al. [18] hypothesized that blocking VEGF might reduce the movement of plasma and water through leaky capillary endothelium into the extracellular space. Surgical resection may be necessary in the case of raised intracranial pressure, if symptoms require rapid control or if symptoms show progression under conservative treatment [24]. In our series, 1 patient remained untreated, the lesion was resected in 1 patient, corticosteroids were given to 2 patients and 1 patient received combination treatment with dexamethasone, bevacizumab and HBO.

Conclusion

RN in children treated for brain tumors can be a potentially severe long-term complication. The discrimination between RN and tumor recurrence still poses a significant diagnostic challenge. Clinical presentation of RN varies from asymptomatic lesions to the development of neurological deficits, which sometimes progress to persistent deficits. Conservative therapeutic management including corticosteroids, HBO or bevacizumab is indicated in patients with neurological symptoms. Surgical intervention might be necessary in patients with life threatening symptoms or those not responding to conservative treatment. There is an urgent need for prospective cooperative group trials to evaluate clinical and functional radioimaging parameters during long-term care of children with brain tumors.

Corresponding address

Dr. V. Strenger
Division of Pediatric Hematology/Oncology,
Medical University of Graz
Auenbruggerplatz 38, 8036 Graz
Austria
volker.strenger@medunigraz.at

Dr. H. Lackner
Division of Pediatric Hematology/Oncology,
Medical University of Graz
Auenbruggerplatz 38, 8036 Graz
Austria

Conflict of interest. V. Strenger, H. Lackner, R. Mayer, P. Sminia, P. Sovinz, M. Mokry, A. Pilhatsch, M. Benesch, W. Schwinger, M. Seidel, D. Sperl, S. Schmidt and C. Urban state that there are no conflicts of interest.

All studies on humans described in the present manuscript were carried out with the approval of the responsible ethics committee and in accordance with national law and the Helsinki Declaration of 1975 (in its current, revised form). Informed consent was obtained from all patients included in studies.

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