UNIL | Université de Lausanne
Faculté de biologie
et de médecine

Mémoire de Maîtrise en médecine No 834

Cavernomas and brain cysts as treatment-related sequelae in survivors of pediatric brain tumors

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Lausanne, 12.12.12

Cavernomas and brain cysts as treatment-related sequelae in survivors of pediatric brain tumors

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Abstract :

Purpose: Cerebral cavernomas as long-term sequelae after radiotherapy are well-known malformations, but cumulative incidence varies between publications, mainly because of the variable MRI techniques used for diagnosis and patients' variable inclusion criteria. Recently researchers tried to compare several predictive factors with the incidence of cavernomas, such as age at radiotherapy and total radiotherapy dose, but results remain controversial. We report on the long-term follow-up of a group of children treated and followed in a uniform way for malignant brain tumors.

Methods: Retrospective study of 36 patients treated for medulloblastoma (22), PNET (3) and ependymoma (11) at our hospital between 1981 and 2009 and followed annually by MRI using T1-, T1gad- and T2-weighted images. The neuroradiologist, radiation oncologist and pediatric oncologist reviewed all radiotherapy charts and MRIs. Predictive factors for cavernoma such as gender and presence of brain cysts were analysed by Chi-square or t-test. Kaplan-Meier method was used to calculate the cumulative incidence.

Results: All patients were < 18 years old at the beginning of radiotherapy and had a median follow-up of 8 years (range 1-18). The total dose of radiotherapy was between 47.4 and 59.4 Gy. Six out of 36 (16.7%) patients developed cavernomas. Cumulative incidence at 1, 5 and 10 years after radiotherapy was 2.8%, 21.9% and 21.9%, respectively. No cavernoma developed in children treated for ependymoma.

There was no statistical association between the predictive factors and occurrence of cavernoma. Fourteen patients (38.9%) developed cysts and the cumulative incidence at 1, 5, and 10 years after radiotherapy was 8%, 37% and 42%, respectively.

Conclusion: Our study confirms cavernomas as late sequelae in patients irradiated for brain tumors. To our surprise, we detected brain cysts at a much higher prevalence compared to cavernoma. To our knowledge, this has never been reported. Their long-term significance and impact on survival has yet to be determined.

Keywords: cavernoma, brain cysts, children, radiation therapy, brain tumors

Introduction:

In the last 25 years the cumulative relative survival (CRS) in children and adolescent treated for medulloblastoma and primitive neuroectodermal tumor (PNET) has improved[1] with an increase of at least 11% of the 5-year and 10-year CRS in children (aged between 1 and 9) and adolescents (aged between 10 and 19). This was even more pronounced in children only where the 5-year CRS increased by 22% between 1981 and 2006. The reasons were on one hand the improvement of treatment associating surgery to radiation therapy and chemotherapy, not only limited to medulloblastoma and PNET but also for the other primary brain tumors of the childhood,[2] and on the other hand the development of better diagnostic tools such as the introduction of magnetic resonance imaging during the second half of the eighties.[3] However, better survival increases the risk of discovering treatment-related anomalies, especially those related to radiation therapy. Cavernoma are such malformations that can develop after radiation therapy.

The main objective of our study was to evaluate retrospectively the incidence of cavernoma and their relationship to treatment, age, gender, tumor type, and radiological anomalies in a population of pediatric patients treated for malignant brain tumors. The second objective was to compare our results to available data of the literature.

Methods:

Retrospective study of all children treated at our hospital between 1981 and 2009 for medulloblastoma, ependymoma and PNET. All patients had a long-term clinical and radiological follow-up by the same team of pediatric oncologist, radiation oncologist and neuroradiologist. Irradiation fields of brain and spine were reviewed for all children and were taken into account during the radiological revision. Radiation techniques at our hospital changed over time with tomotherapy replacing the linear accelerator in 2007. Cerebrospinal magnetic resonance imaging (MRI) was used for follow-up and performed before 1994 every 6 months until 2 years and then yearly. After 1994 follow-up was done every 3 months during the first year, then at least every 6 months until 3 years of follow-up and then yearly until at least 10 years after the end of treatment.

MRI images comprised at least T1, T2 sequences and T1 after gadolinium injection executed on a 1.5 or 3 T scanner with a slice thickness between 5 and 3 mm. T2* sequences were added in the follow-up of children when cavernomas were detected.

After reviewing the preoperative and postoperative MRI, the last available MRI was evaluated in search of cavernoma, diffuse white matter lesions (DWMLs) and brain cysts. The timing of

appearances, and the aspect of these lesions were recorded. The typical MRI aspect of cavernoma was considered to be a heterogeneous signal, with a centre of hyper-intensity on T2-weighted images, that corresponds to haemoglobin degradation products, surrounded by a hypo-intensity signal on T2-weighted imaging corresponding to rests of hemosiderin. The typical aspect on MRI of brain cysts was an oval lesion showing signal hyper-intensity on T2–weighted images with a thin wall enhancing contrast. The DWML classical MRI presentation was a diffuse hyper-intensity signal on T2-weighted imaging of the white matter.
Localisations of cavernomas and DWMLs were divided in subtentorial vs. supratentorial sites. The localisation of cysts was precisely recorded.

Age at radiotherapy, gender, tumor type, dose of craniospinal irradiation, dose of the radiation boost applied to the posterior fossa, DWML development and brain cysts presence were analysed with the appearance of cavernoma. The relationship of the latter to cavernomas was statistically analysed in two ways: First of all the proportion of cysts among the patients presenting with cavernoma compared to the patients without (non-cavernoma group) and subsequently we analysed the latency period for development of cysts in the last two groups. All the predictive factors were analysed by using the "R" statistical program, precisely by the way of the Chi-square or the t-test.
We calculated the cumulative incidence of cavernoma and brain cysts at 1, 5 and 10 years after radiotherapy by the Kaplan-Meier method.

Results:

Between 1981 and 2009 62 patients were treated for malignat brain tumors (34 medulloblastoma, 10 PNET and 18 ependymoma), but only 36 were selected for evaluation (22 medulloblatoma, 3 PNET and 11 ependymoma), 17 boys and 19 girls. Eleven patients died of disease during the first years of follow-up and were not included. Preoperative sequences and/or follow-up MRI sequences weren't found in 12 cases. Tree children were excluded because they did not receive radiotherapy, because of their extremely young age at diagnosis (2 and 4 months respectively) and the last patient didn't benefit from radiotherapy for unknown reasons.
Seven patients died of primary disease (4 medulloblastoma, 2 PNET and 1 ependymoma) and 2 died (ependymomas) of secondary malignancy.
The median age was 6.42 years (range 1.25-18.5) and their median imaging follow-up since end of radiotherapy was 8 years (range 1-18). Except one patient, who died before the surgery, all other children had a complete or sub-complete tumor resection before the start of

radiotherapy. Twenty-four out of 36 (66%) were treated with neo-adjuvant or adjuvant chemotherapy. Among the patients with medulloblastoma, only 4/22 patients (18%) were not treated with chemotherapy before the beginning or after the end of irradiation therapy. All patients affected by PNET (3) received neo-adjuvant chemotherapy. Due to ependymomas' chemotherapy resistance, only 3/11 (27%), who could not benefit from a total resection, received neo-adjuvant chemotherapy. Ependymoma was located in the posterior fossa in 9/11 patients (81.8%).

All patients received a daily dose between 1.6 and 1.8 Gy and the photon energy was 6 MV. Four patients (11.1%) of this study could benefit from tomotherapy as irradiation technique. Craniospinal irradiation with a boost to the posterior fossa was used for patients having medulloblastoma (22), one patient with subtentorial ependymoma with meningeal dissemination at diagnosis and one patient with PNET (case 4 of Table 1). The remaining ependymomas (10) and PNETs (2) had only local irradiation to the primary tumor site. The mean dose received at the tumor area was 54.6 Gy (range 47.4-59.4).

By the analysis of MRI sequences before the radiotherapy, we found only 2 children with developmental venous anomaly (DVA). Six patients developed cavernomas (16.7%) with a cumulative incidence at 1, 5, and 10 years of follow-up after radiotherapy of 2.8%, 21.9% and still 21.9% respectively. The probability of remaining cavernoma-free over time is illustrated in Figure 1. Because of increasing use of T2*-weighted images for detection of cavernoma, we could identify other smaller cavernomas in these patients, but these were not included in the results of this study. The median latency period for first detection of cavernoma by MRI was 4 years (range 1-4). The median radiological follow-up was similar between the non-cavernoma group (Figure 2) and cavernoma group of children (Figure 3), with a value of 8 years (range 1-18) and 9.5 years (range 6-15) respectively. Two patients presented neurological symptoms related to bleeding in the cavernoma resulting in surgical intervention. One patient presented a cavernoma in association with a DVA (Case 1 of Table 1). This patient has been reported previously by Maeder, et al.[4] We found a total of 19 cavernomas, three (15.8%) of them localized in the brain boost zone. The complete clinical data are summarized in Table 1.

Brain cysts were found in 14/36 patients corresponding to a prevalence of 38.9% and a cumulative incidence at 1, 5 and 10 years after radiotherapy of 8%, 37% and 42% respectively. The probability of cyst-free follow-up is illustrated in Figure 1. DWML developed in 16/36 patients (44.4%). They were located in both cerebrum and cerebellum in 2 patients, cerebellum only in other 2 patients and in cerebrum only in 12 patients.

Among the predictive factors studied, none was significantly (p-value<0.05) associated with the development of cavernoma (Table 2). Because of a very similar mean age in the cavernoma group (6.9 years) and in the non-cavernoma group (7.1 years) of patients, we considered statistical analysis of this variable as risk factor for cavernoma as unnecessary. No cavernoma was observed in children treated for ependymoma. The mean boost dose was greater in the non-cavernoma group of patients, so that its role as a predictive factor for vascular malformations could be ruled out (Table 3). The lowest p-value in our study (0.15) concerned the mean latency period for detection of brain cysts after radiotherapy with a mean interval of 4.1 years (range 0.3-13).

Discussion:

Well-recognized late secondary effects of radiations on the brain are: diffuse white matter injury,[5,6] cerebral-vascular effects,[7,8] glioma[9,10] and meningioma.[10,11] This in addition to the risk of primary tumor recurrence and secondary radio-induced malignancy motivates a follow-up by imaging. There is increasing evidence of cavernoma as a possible long-term consequence of radiotherapy, but the mechanism is not clearly understood. In 1998 Maeder, et al.,[4] reported a case of a child irradiated for a medulloblastoma who developed a cavernoma in anatomical association with a DVA. The hypothesis was that radiation caused a stenosis of the DVA with consecutive elevation of the pressure and this event brought to cavernoma development. In 2004 Lee, et al.,[12] histologically proved the presence of radiation induced vasculopathy (intimal hypertrophy and fragmentation of the elastic laminae with hyline sclerosis) in an acute hematoma-wall (with an underlying vascular malformation) of a woman treated at a young age with radiotherapy for medulloblastoma. As cavernoma consist of a compact mass of sinusoidal-type vessels in the white matter[13] the hypothesis is, that they result from vascular injuries due to radiotherapy associated with stimulation of angiogenesis.[8]

Cavernoma are mostly asymptomatic[14,15,16] but can cause symptoms in case of hemorrhage. Nimjee, et al.,[17] found that in case of symptomatic cavernoma, the most frequent presentations were seizures and headaches. The mass effect of hemorrhage of a cavernoma is rarely so important to need a surgical intervention, but Lew, et al.,[15] have reported the case of a boy treated with radiotherapy at the age of 6 years, who presented seizures 5 years later. The reason was a hemorrhage resulting from 2 cavernomas in the left frontal lobe causing significant mass effect and requiring craniotomy.

Several groups studied radiation-induced cavernomas focusing on incidence, prevalence and lag time after radiotherapy.

Our study showed a prevalence of cavernoma of 16.7% which is between the reports by Burn, et al.,[14] with 3.4%, Strenger, et al.,[16] with 4.7% and Lew, et al.,[15] with 31%. We found a cumulative incidence of 21.9% at 10 years after radiotherapy, which is also between the 3.9% reported by Strenger and the 43% reported by Lew.

The cumulative incidence increases over years, but our lower values compared to Lew, et al.,[15] can be explained mainly by the fact that they used in their recent study (2007) focused on medulloblastoma (59) also the diffusion-weighted MRI sequence which has an higher sensivity for cavernoma detection. The radiological follow-up probably didn't play a role because our mean follow-up of 8.0 years was similar to theirs of 7.2 years. Our study included only patients with a minimal radiological follow-up of 1 year, similar to this last author's study.

In contrast, we found more cavernoma compared to Burn, et al.,[14] and Strenger, et al.,[16] and the explication lies in patients' selection criteria. Compared to Burn, et al.,[14] who also focused only on brain tumors (297), their radiological follow-up could probably explain the difference of prevalence (they didn't take into account the cumulative incidence). Although the mean or median duration of radiological follow-up wasn't reported, the minimal radiological follow-up of their study accounted for only 1 month and the median lag time before first cavernoma detection after radiotherapy was the shortest found in the literature and counted for 3 years (range 0.25-8.5). We found a median lag time before first cavernoma detection of 4.0 years (range 1-4) and our period of study was longer with 28 years compared to 16 years. So the longer observation period could explain the higher prevalence of cavernoma in our cohort.

If on one hand, the radiological follow-up didn't probably play a role to explain our higher results compared to Strenger, et al.,[16] as they had the longest median radiological follow-up found in the literature (14.6 years), almost twice as long as in our study, on the other hand half of the patients of this cohort were leukaemia patients who received usually doses of radiotherapy lower than 30 Gy which is clearly less compared to brain tumor patients. The threshold of 30 Gy is considered by Heckl, et al.,[18] as a significant risk factor of cavernoma, but this fact wasn't confirmed by Strengers' et al.,[16] data. In 2002 Heckl, et al.,[18] analysed the total radiotherapy dose role in relation with the latency period between the age at the irradiation treatment and the moment of cavernoma diagnosis. They analysed 40 children that developed cavernomas after cranial irradiation not only in reason of primary brain tumors. They found a significant correlation (p=0.0018 using Wilcoxon test) resulting in a shorter period of latency,

when the radiotherapy dosage surpassed 30 Gy. In conclusion, our prevalence and cumulative incidence could be useful to complete the epidemiologic notions concerning these late vascular consequences of radiotherapy.

Until now, researchers tried to compare several predictive factors with the incidence of cavernoma, such as age at radiotherapy,[14,15,16,18] gender,[15,16] type of cancer,[16] cranial zone of highest irradiation[15,16] and chemotherapy.[14,15,16] As our study comprised only brain tumors patients, they all were above the controversial risk factor-threshold of 30 Gy of the total radiotherapy dose. One of our goals was to analyse, as risk factor, the craniospinal dose and the boost dose on the posterior fossa. Only Lew, et al.,[15] tried to analyse the craniospinal dose as a risk factor of cavernoma, finding no significant effect. To analyse this last factor we excluded all patients who had not craniospinal irradiation as a total of 12 children (10 ependymoma and 2 PNET), finding no relationship (Table 2). Surprisingly we found a slightly higher result of the mean boost dosage (Table 2) in the non-cavernoma group of patients (after the exclusion, as for the craniospinal dose, of 10 ependymoma and 2 PNET) and so we didn't calculate the p-value for this variable. No other significant association have been recorded in the literature, except a statistically significant growing incidence when the radiotherapy was started in the first decade.[16,18] Concerning the age at the radiotherapy, our result supports the conclusions of Burn, et al.,[14] and Lew, et al.,[15] finding no relation with cavernoma formation. In our study, neither the fact to be affected by a medulloblastoma was a risk factor of cavernoma (p-value 0.44). Only the 15.8 % of all cavernomas were situated in the brain boost zone (area with the highest total radiotherapy dose). A similar result (23%) was obtained in the study restricted to medulloblastoma.[15]

Concerning cerebral anomalies, we analysed as a risk factor of radiation-induced cavernoma the DWML of cerebellum or cerebrum and brain cysts development. The first anomaly is well known as a subacute (months post irradiation) or late (years post irradiation) effect of brain radiation therapy, but chemotherapy could have an additional effect.[5,6] Our data exclude the association with cavernomas (p-value 1.0). We didn't calculate the cumulative incidence for this cerebral anomaly because of the spontaneous regression, in 5 patients, of the radiological presentation in the cerebellum and/or cerebrum. Therefore it was interesting to note that on the total of 6 children that developed a sub-acute DWML, only one didn't have a previous chemotherapy. We reported also that 3 children presented a DWML before the start of radiotherapy, which could be due to neo-adjuvant chemotherapy. It is possible that some patients in our study, who didn't present cerebral abnormalities in both pre-irradiation and in

the last available sequences, developed a transitory DWML. So our prevalence of DWML (44%) may be under valuated.

Surprisingly we encountered a high prevalence of brain cysts with 14/36 patients (38.8%), but however not statistically significant as a risk factor of cavernoma. Their aetiology remain unclear, but in 2001 Brandsma, et al.,[19] reported an adult patient developing multiple cysts in the cerebrum, 4.5 years after the radiation therapy for a unique cerebellar metastasis of lung carcinoma. As described by authors, brain cysts started to develop on the DWML several years after the MRI detection of this last cerebral anomaly suggesting that cerebral cysts could be a late stage of DWML after irradiation therapy. In 2009 Wang, et al.,[20] analysed temporal lobes of adult survivors (124) of nasopharyngeal carcinoma who received radiation therapy. The radiation field included the skull base, the inferior and medial parts of temporal lobes. They found brains cysts always in presence of DWML of temporal lobes, and frequently (74%) brains cysts developed after DWML. So, concerning adults, there is an increasing evidence of brains cysts as a possible long-term stage of DWML.

We recorded a total of 25 brain cysts and 7/25 (28%) were situated in the DWML area. Concerning children, in 2005 Kitajima, et al.,[21] described asymptomatic brain cysts formation after cranial irradiation for primary brain tumors. They reported that 18.2% (6) of children developed one or more cystic lesions and the mean latency after radiotherapy was 2.6 years (range 1.5-7). It is interesting to notice that we had more than double percentage of patients with cysts development, though we had a lot of methodological and clinical common points with this last study: we had a comparable total mean radiation dose (54.59 Gy vs. 48.7 Gy[21]), mean age of patients at the radiotherapy (7.1 years vs. 6.9 years[21]) and number of patients (36 vs. 33[21]). One explication could be significantly longer mean radiological follow-up in our study with 8.0 years (range 1-18) in contrast to 4.8 year (range 0.5-16) of the Japanese group. The MR imaging sensibility for cysts development didn't probably play a role to explain the described differences because it was greater in the publication of Kitajima, et al.,[21] in reason of a lower slice thickness utilized for axial images of T1, T1gad and T2 sequences than in our study. It's interesting to note that in Kitajima's study only one patient (3%) developed "an hemorrhagic change suggestive of telangiectasia", and this patient was one of the six children presenting a cystic change. So we could not exclude that our higher prevalence of cavernoma could play a role to explain our higher brain cysts prevalence (Figure 4 as example).

Furthermore brain cysts seem not to bee related to medulloblastoma. Our study counted 61% (22/36) of medulloblastoma but only 36% (8/22) of these last developed brain cysts, otherwise 43% (6/14) of children affected by remaining primary brain tumors developed

brain cysts. This affirmation is supported by the mean duration of radiological follow-up, which was longer in the medulloblastoma group (8.9 years) than that of the non-medulloblastoma group of patients (6.7 years). So, the higher proportion of medulloblastoma of our research compared to 24% (8/33) of Kitajima et al.,[21] became noteworthy. Despite the fact that brains cysts, do not appear as a risk factor of cavernoma, they seem to represent another entity of sequelae related to radiotherapy and their prevalence was higher compared to cavernoma.

Compared to other studies, our group of 6 patients presenting cavernomas is comparable (eight in the study of Strenger, et al.,[16] ten in the one of Burn, et al.,[14] and eighteen in the one of Lew, et al.[15]), but 30 patients without cavernoma (concerning statistical analysis of radiotherapy mean doses the non-cavernoma group counted only 18 children) much smaller (163 in the first,[16] 287 in the second[14] and 41 in the last[15] just in sequence cited researches).

Conclusions:

Increasingly children affected by brain malignant brain tumors survive and develop cerebral sequelae. Our study confirms cavernomas as late sequelae in patients irradiated for brain tumors. Through these vascular malformations are more often asymptomatic and benign in their evolution, the subsequent hemorrhages must be suspected in a child known as a cavernoma carrier, especially in case of seizures and headache.[17] The role of different risk factors for the development of cavernoma remains controversial and they could only marginally aid the clinician. To our surprise, we detected brain cysts, as a distinct entity, at a much higher prevalence compared to cavernoma. To our knowledge, this phenomenon has never been reported in the literature. Their long-term significance and impact on survival has yet to be determined and longer follow-up of these patients is needed.

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Fig.1. *Probability of resting lesion-free after radiotherapy*

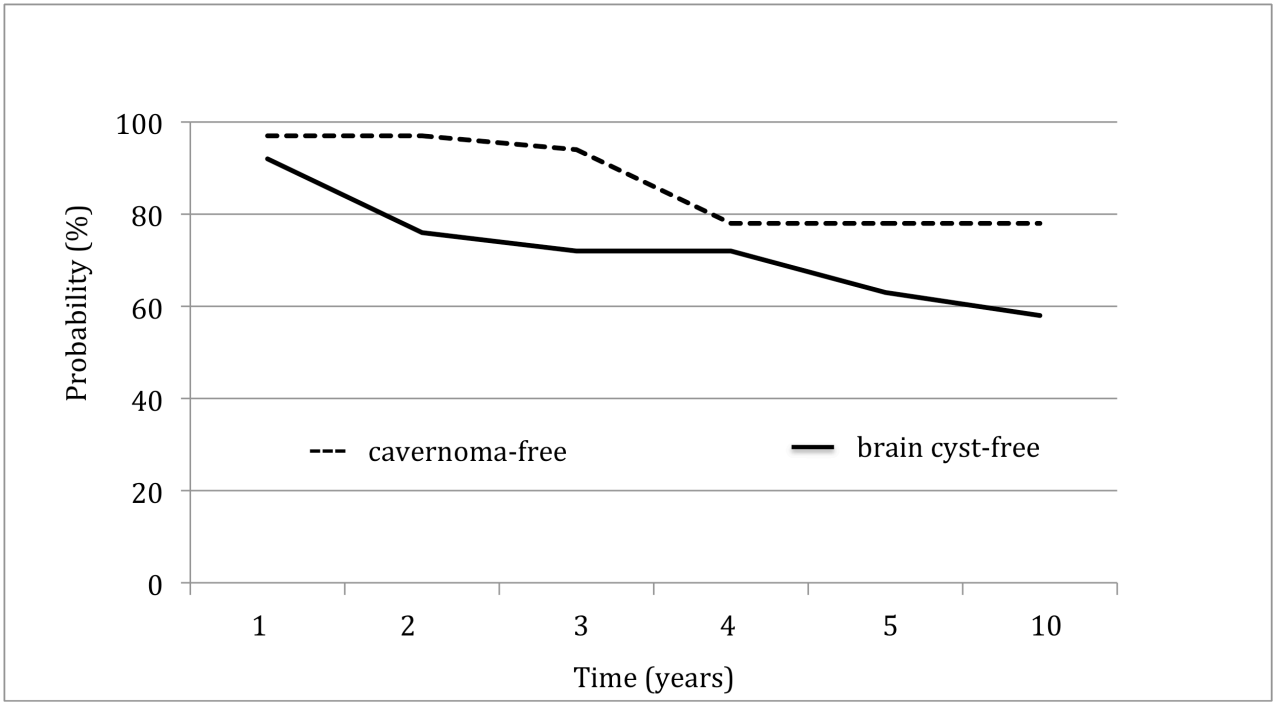


Fig. 2. Radiological follow-up after radiotherapy and lesion detection in the non-cavernoma group

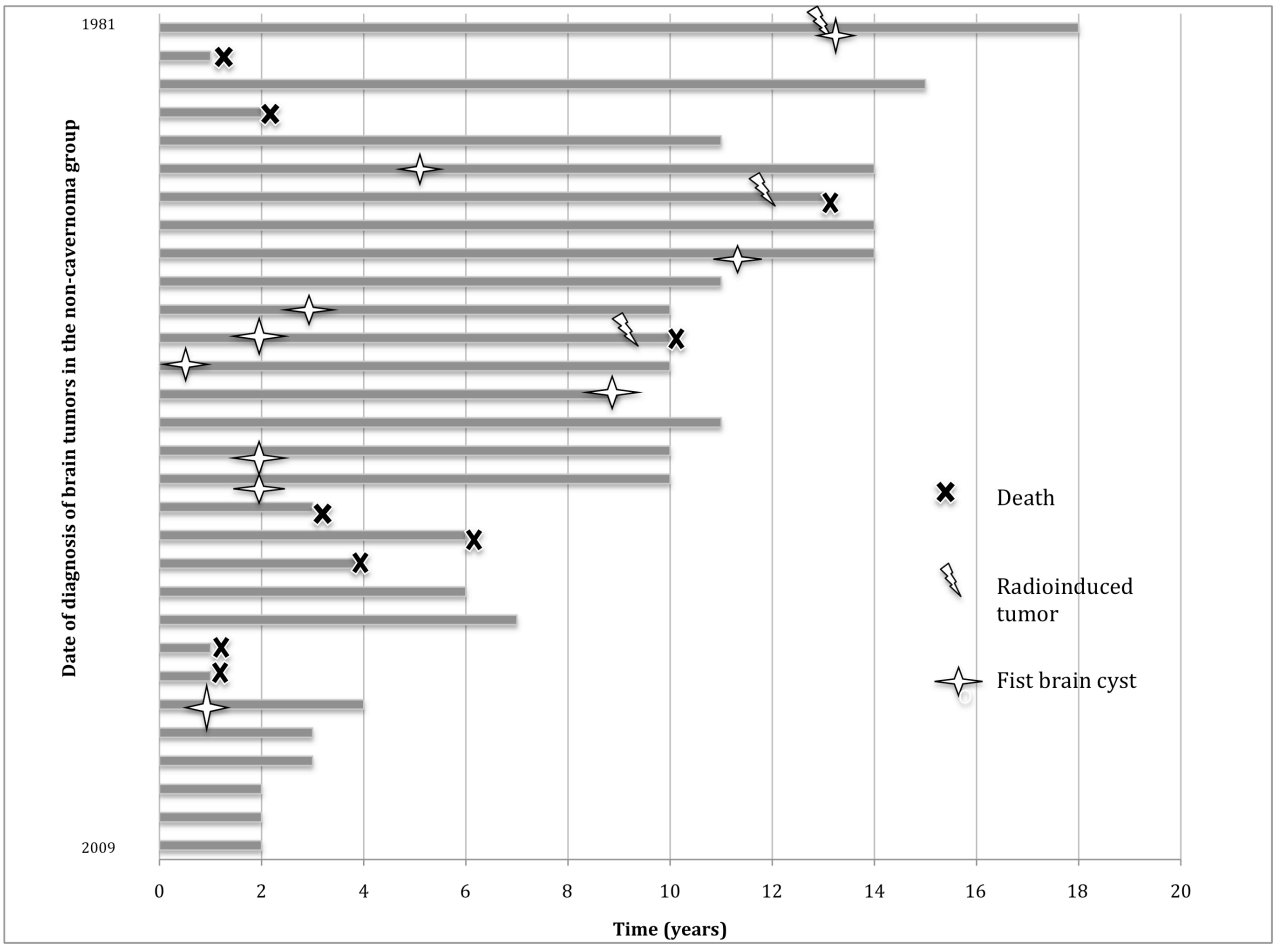


Fig. 3. Radiological follow-up after radiotherapy and lesion detection in the cavernoma group

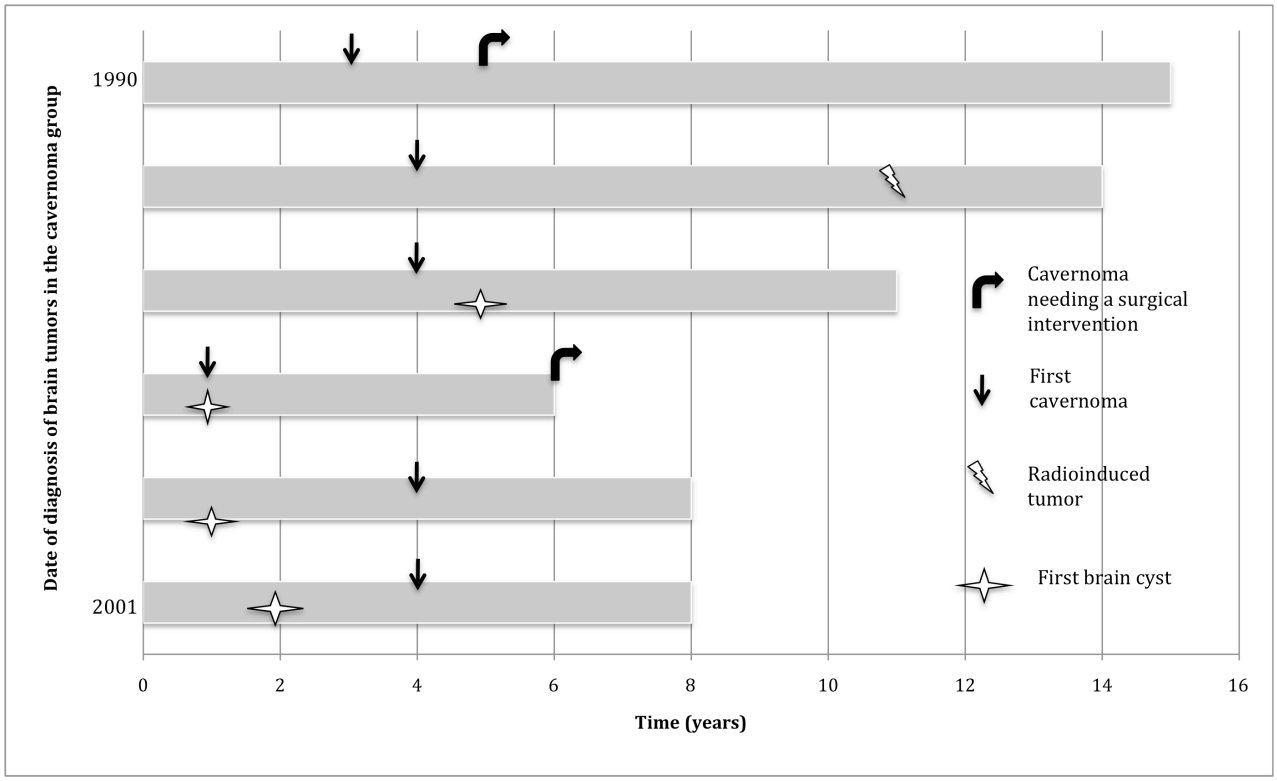
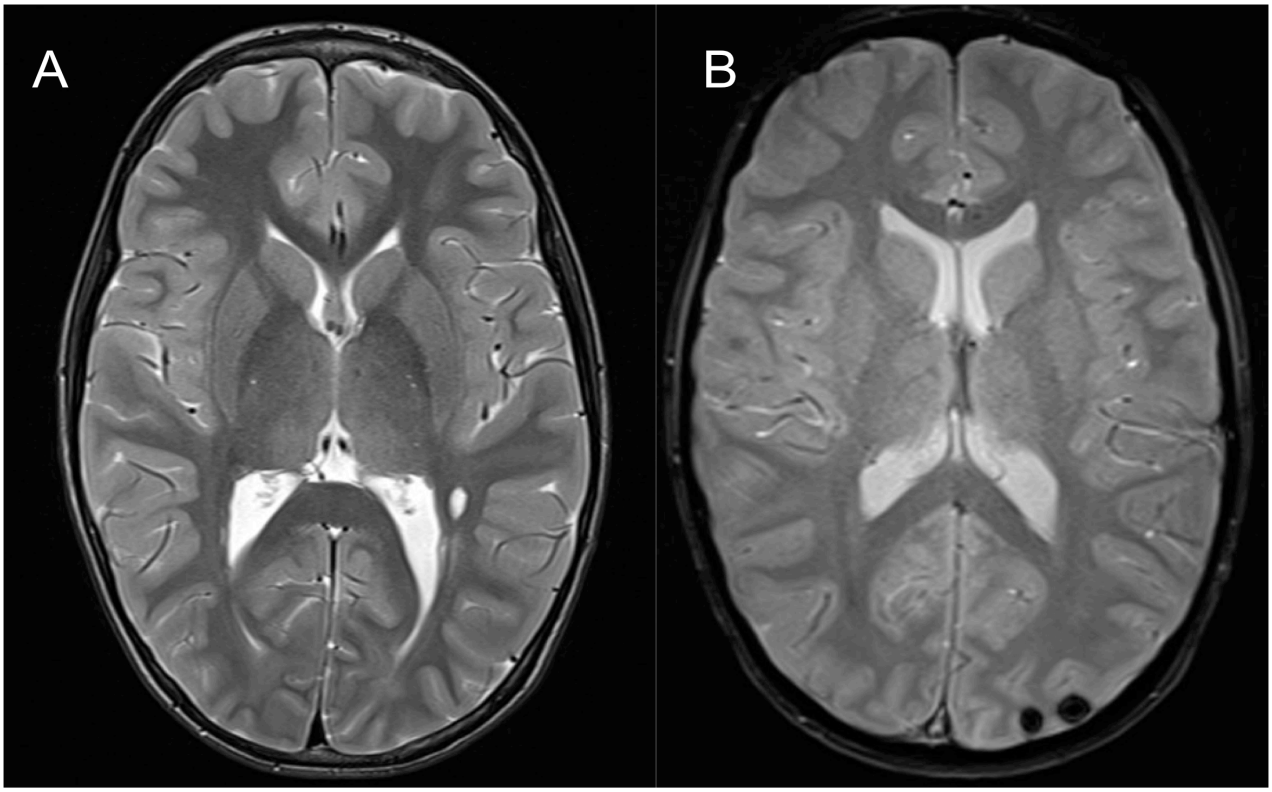


Fig 4. Case 5. Axial T2-weighted MRI showing a brain cyst in the paraventricular left white matter [A] and axial T2-weighted MRI demonstrating 2 left occipital cavernomas [B]*



Tab. 1. Cavernomas in 6 patients

Case No.	Sex	Age at the radiothe-rapy (years)	Diagnosis	Latency period to cavernoma detection (years)	No. of detected caverno-ma	Cavernomas localisation (supra vs. subtentorial)	Presence of symptoms that led to a surgical intervention
1	male	8.25	medulloblastoma	3	1	supratentorial	yes
2	female	6.42	medulloblastoma	4	1	subtentorial	no
3	male	7.66	medulloblastoma	4	8	both	no
4	male	4.75	PNET	1	2	both	yes
5	male	4.33	medulloblastoma	4	4	both	no
6	female	10.25	medulloblastoma	4	3	both	no

Tab. 2. Predictive factors and cavernomas

	Cavernoma (6 patients)	Non-cavernoma (30 patients)	Total (36 patients)	Statistic method	Value
Male sex (%)	66.7 (4)	43.3 (13)	47.2 (17)	CHI square	0.55
Medulloblastoma (%)	83.3 (5)	56.7 (17)	61.1 (22)	CHI square	0.44
Radiation mean dose (Gy) of craniospinal field (22 medulloblastoma, 1 PNET, 1 ependymoma)	33.2 (6)	30.6 (18)	31.2 (24)	Welch t-test	0.52
Brain cysts (%)	66.7 (4)	33.3 (10)	38.9 (14)	CHI square	0.28
Mean latency period after radiotherapy for brain cysts detection (years)	2.3 (4)	4.8 (10)	4.1 (14)	Welch t-test	0.15
Diffuse white matter lesion (%)	50 (3)	43 (13)	44 (16)	CHI square	1

Tab. 3. Characteristics of radiotherapy

	Cavernoma group (6)	Non-cavernoma Group (30)	Total (36)
Mean total dose (Gy) concerning all patients	55.3 (6)	54.5 (30)	54.6 (36)
Mean craniospinal dose (Gy) concerning medulloblastomas, 1 ependymoma and 1 PNET	33.2 (6)	30.6 (18)	31.2 (24)
Mean boost dose on the posterior fossa (Gy) concerning medulloblastomas, 1 ependymoma and 1 PNET	22.2 (6)	24 (18)	23.6 (24)