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Reirradiation of relapsed brain tumors in children

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ABSTRACT

Aim: The aim of this study was to evaluate toxicity and response to fractionated reirradiation (FR) of relapsed primary brain tumors in children.

Background: The treatment options for recurrent brain tumors in children previously irradiated are limited. Reirradiation is performed with fear due to the cumulative late CNS toxicity and the lack of a significant chance of cure.

Materials and methods: Between 2008 and 2009, eight children with a median age of 14.5 years with a diagnosis of a recurrent brain tumor underwent reirradiation. Initially, all patients were treated with surgery, chemotherapy and radiotherapy. The median time to the first recurrence after the initial treatment was 19.5 months. Intervals between radiotherapy courses were in the range of 5–51 mos. All retreatments were carried out with 3D image-based conformal methods. The total prescription dose was 40 Gy in a fraction of 5×2 Gy/week. The total cumulative dose ranged from 65 to 95 Gy (median: 75 Gy). The median cumulative biologically effective dose was 144 Gy (range: 126–181 Gy).

Results: The median overall survival and progression free survival measured from the beginning of reirradiation was 17.5 and 6.5 months, respectively. During the first evaluation, four patients showed a complete or partial response, two did not respond radiologically. Two children were progressive at the time of reirradiation. Among children with progression that occurred during the first year after reirradiation, only two progressed in the treatment area. The repeated irradiation was well tolerated by all patients. No late complications have been observed.

Conclusion: In the absence of other treatment possibilities, the fractionated reirradiation with highly conformal three-dimensional planning could be a therapeutic choice in case of recurrent brain tumors in children. The control of craniospinal dissemination remains to be the main problem.

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1. Background

Central nervous system (CNS) tumors account for about 20% of all childhood malignancies. Notwithstanding the advances in the treatment of pediatric brain tumors, in particular medulloblastoma, in most series 30–40% of patients develop recurrences which result in death due to tumor progression.[1]

The treatment options for recurrent brain tumors in children previously irradiated are limited. Reoperation and standard dose salvage chemotherapy are used in majority of these patients providing a palliative effect. Reirradiation within the central nervous system may result in temporary local control but is performed with fear due to cumulative late CNS toxicity and the lack of a significant chance of cure. It may be offered only to selected patients with lesions of limited size localized in a "safe" area. This is particularly important in the treatment of children. In the literature there are only few publications concerning this topic. New conformal radiotherapy techniques allow reduction of the treatment volume thereby sparing normal tissue, which consequently decreases the risk of the late toxicity.[2–6] Additionally, radiobiological data suggest at least partial repair of CNS radiation damage after the initial course of radiotherapy. The magnitude of this recovery depends on the total dose and fractionation regimen in the first course and the time elapsed between treatments. Despite this fact, many different reirradiation treatment schemes are used with regard to total dose, size and number of fractions.[7,8]

Due to the low repair capacity of the brain tissue, reflected in the α/β ratio, which is estimated to be approximately 2 Gy, the biologically effective dose (BED) rather than the "physical" irradiation dose, should be considered in the analysis of radiotherapy protocols.[9] Our data were analyzed using this cumulative BED, which is the sum of the BED of the initial irradiation course and the BED of the reirradiation course.

2. Aim

The aim of this study was to evaluate toxicity and response to fractionated reirradiation (FR) of relapsed primary brain tumors in children.

3. Materials and methods

3.1. *Patients*

In the period from January 2008 to September 2009, eight children (5 male, 3 female) with a median age of 14.5 years (range 9–18.5 years) with a diagnosis of a recurrent brain tumor underwent reirradiation at the Radiotherapy Department of MSCM Cancer Centre in Warsaw. Both the clinical data and radiotherapy technical records were reviewed.

The primary histological diagnoses included: six medulloblastoma (MB), one germ cell tumor (GCT) and one non-germ cell tumor (NGCT). Five patients with medulloblastoma were classified as a high risk group, only one (pt. 2 in Table 1) as standard risk.

Table 1 – Children retreatment data.

No.	Histology	RT1 volume	RT1 dose total/fraction [Gy]	RT2 volume	$V_{PTV(RT2)}$ [ccm]	RT2 dose total/fraction [Gy]	TD cum. [Gy]	BED cum. [Gy]	Interval RT1–RT2 [mos]	PFS [mos]	OS [mos]/ outcome	Time to PTV failure [mos]
1	MB	CNS	35.07/1.67	PFT-rec.	4.8	40/2	95	181	51	14	27	21
		TB	55.11/1.67								CNS-meta	
2	MB	CNS	25.05/1.67	Occipital-meta	7.9	40/2	65	126	44	12	26	19
		TB	55.11/1.67	PFT-rec.	15.1	40/2	95	181	50		CNS-meta	
3	NGCT	VS	30.6/1.8	Spine-elective		30.6/1.8			5	5	12	Without LP
		TB	54/1.8	PFT-meta	22.3	40/2	71	138			Death	
4	MB	CNS	35.07 (spine: 40.08)/1.67	Frontal-meta	33.9	40/2	75	144	39	6	17	6
		TB	55.11/1.67								CR	
5	MB	CNS	35.07/1.67	Frontal-meta	8.3	40/2	75	144	39	7	18	Without LP
		TB	55.11/1.67								Spine-meta	
6	MB	CNS	35.07/1.67	PFT-rec.	60.5	28/2	83	157	33	1	6	1
		TB	55.11/1.67								Death	
7	MB	CNS	35.07/1.67	VS-meta	20.4	40/2	75	144	27	1	19	Without LP
		TB	55.11/1.67								VS-meta	
8	GCT	VS	24/1.6	Brain-elective		18/1.8			35	9	9	Without LP
		TB	40/1.6	VS-meta	46.5	40/2	80	152			PR	

RT1, first radiation course; RT2, second radiation course; PFT, posterior fossa tumor; TB, tumor boost; VS, ventricular system; LP, local progression.

Initially, all patients were treated with surgery, chemotherapy and radiotherapy. The radiotherapy doses were to the central nervous system, ranging from 25.05 to 35.07 Gy with a posterior fossa tumor bed boost to a total dose of 55.11 Gy (6 pts. with MB), and to the ventricle system (VS) of 24 and 30.6 Gy with a primary tumor region boost of up to 40 and 54 Gy (2 pts. with GCT and NGCT).

All patients with recurrent tumors were evaluated with contrast-enhanced cranial and spine MRI. A relapse was defined as the progression of neoplasm at the original site or the occurrence of a new tumor elsewhere. The disease relapse was located in the tumor bed only in 2 children. In the other cases, it appeared as an isolated metastasis in the brain in 3 patients and as multifocal in the remaining 3. No patient had dissemination in the spine. The median time to the first evidence of recurrence after the prior treatment was 19.5 months (range: 2–47 mos).

3.2. *Retreatment*

At the time of tumor recurrence, only one patient was treated with surgery. Seven children received salvage conventional chemotherapy including multidrug regimens such as: ETIF (etoposide, uromitexan, ifosfamide), ICE (ifosfamide, carboplatin, etoposide), Temodal + Irinotecan, Vepesid + Ifosfamid/DTIC and PVB (cisplatin, vinblastine, bleomycine). Reirradiation was given with the intent to consolidate the effect of chemotherapy. Intervals between radiotherapy courses were in the range of 5–51 months (median: 39 months). Six patients with MB were reirradiated for recurrent tumors only. In the two remaining cases, the irradiated volume was larger. In the patient with NGCT, a prophylactic irradiation of the spine was performed additionally. The patient with GCT was first irradiated for the whole brain due to the multifocal relapse. All reirradiated volumes comprised previously irradiated areas. Retreatment was carried out with 3D image-based conformal methods. The gross tumor volume (GTV) was contoured by using the option of fusion images of CT and diagnostic MRI scans. The GTV was defined by contrast enhancing area on T2-weighted MRI-images. The planning target volume (PTV) consisted of the GTV with a 4 mm safety margin. Mean PTV was 24.4 ccm (range: 4.8–60.5 ccm). Summary (initial and retreatment) dose-volume histograms (DVHs) for non-target brain were compared for various plans and beam orientations which minimized normal brain tissue irradiation were selected. DVHs for organs at risk such as brain stem or visual pathway were particularly evaluated because of the risk of life-threatening complications. Our goal was to reduce the dose in these structures. Doses from reirradiation are presented in Table 2.

Two to six fields formed by a multileaf collimator were applied. In treatment plans, the high dose homogeneity was achieved: $D_{max} < 105\%$ was obtained in all plans, $D_{min} > 93\%$ was received in 7 plans; in the other two, D_{min} was lower because of the vicinity to the brain stem.

FR was delivered using a linear accelerator with 4, 6 and 15 MV photons. The total prescription dose was 40 Gy in 2 Gy daily fractions. The total cumulative dose (TD_{cum}) ranged from 65 to 95 Gy (median: 75 Gy). The median cumulative BED was 144 Gy (range 126–181 Gy). All children completed the second course of radiotherapy, except one girl. Neurological condition of this girl worsened during reirradiation. The MRI showed disease progression in the brain and we finished the treatment after dose of 28 Gy.

The kilovoltage cone-beam CT was performed before the first and second reirradiation fraction and once weekly thereafter. The correction of the isocenter position was done when the offset results were >2 mm. Salvage chemotherapy based on various regimens was applied in all children after repeated radiotherapy.

3.3. *Follow-up*

During the follow-up, all patients were seen at regular intervals. The first neurological examination and MRI were performed 1–3 months following reirradiation, then at 3–4 months intervals in the first post-radiotherapy year, and at 5–6 month intervals thereafter.

Central nervous system toxicity was defined as the development of any new neurologic symptoms (with or without MRI abnormalities) after radiotherapy that may be attributed to this treatment. Toxicity was defined as acute when occurring within 3 months after treatment and chronic when occurring after more than 3 months. The Radiation Therapy Oncology Group (RTOG) CNS toxicity criteria were used to assess the toxicity of the treatment.

4. Results

The evaluation was completed with a median follow-up of 16 months (range 6–27 mos). No patient was lost during the follow-up. The median overall survival (OS) and progression free survival (PFS) measured from the beginning of reirradiation was 17.5 and 6.5 months, respectively. Results are showed in Table 1.

The radiological response was assessed in all patients. During the first evaluation after the retreatment, four patients

Table 2 – Reirradiation doses in brain stem and optic pathway [cGy].

	1	2	3	4	5	6	7	8
Brain stem (D_{av}/D_{max})	37/75	887/3793	47/78	17/31	28/49	348/3474	17/28	1840/2163
Optic pathway (D_{av})	11	42	13	48	99	20	208	2042

D_{av}, average dose; D_{max}, maximum dose.

showed a complete or partial response, two did not respond radiologically. Two children were progressive at the time of reirradiation. One of these patients died 5 months after the end of reirradiation due to the CNS dissemination. The second child who died after 12 months was the patient with NGCT. He had the non-local intracranial progression. Six other patients are still alive, one with complete remission, one with partial remission and 4 with progression. Among children with progression that occurred during the first year after reirradiation, only two progressed in the treatment area. In the other cases, there was a spread in the brain (2), spine (1) or throughout the CNS (1) without progression in the irradiated field.

The repeated irradiation was well tolerated by all patients. No grade 3–5 acute toxicity was detected. Four children had mild symptoms of radiotherapy toxicity (grade 1) not requiring medication, the other four had headache and vomiting that required steroids in low doses and/or antiemetic treatment (grade 2). No severe late complications of reirradiation have been observed. Children retained a satisfactory functional status. 95% confidence interval for the probability of late complications ranged from zero to 0.375 (0; 0.375).

5. Discussion

Reirradiation used in the management of recurrent brain tumors in adults and children is a controversial issue. This method may result in a temporary local tumor control but carries the risk of a late central nervous system damage. We have not performed the reirradiation in children before 2008 for fear of the occurrence of serious complications of this treatment. Decision of how to carry out the retreatment is a complex process. The tolerance dose of normal brain tissue to a single course of radiotherapy is estimated to be 50–60 Gy in 2 Gy daily fractions. Less is known about the tolerance to the second course.[7] There are no experimental data available on reirradiation tolerance of the brain. But some clinical series suggest that the reirradiation of the brain may be associated with a lower incidence of severe complications then previously feared. The following factors are taken into account when planning the retreatment: type of tissue exposed to damage, fractionation regimen, interval from previous irradiation, observable normal tissue changes resulting from previous irradiation and patient's life expectancy.[8] Other suggested risk factors for radiation necrosis include: chemotherapy use, lower conformality index, shorter overall treatment time, older age and diabetes mellitus.[10]

Although location does not influence the susceptibility to radiation necrosis, necrosis is far more likely to be symptomatic in certain areas, e.g. the corpus callosum and brain stem.[10] Therefore the location of PTV and its volume often influence the choice of reirradiation technique.[11] Our current radiotherapy technique for retreatment utilizes multiple, noncoplanar 3D conformal beam arrangements which minimize the overlap with previously irradiated volumes, especially in the brain stem. Earlier, some authors used the whole brain irradiation or a simple technique with opposed fields. However, in their series a higher risk of toxicity was stated.[7,12]

In all our patients, we planned the reirradiation dose of 40 Gy in 2 Gy daily fractions. The argumentation for this dose level was two-fold. Firstly, several studies have demonstrated no severe brain injury in patients treated with cumulative doses of up to 100 Gy (2 Gy daily fractions; BED 200 Gy). Secondly, the dose of reirradiation course should be high enough to obtain temporary local tumor control.[7,9,13]

In the overview of current clinical data on reirradiation of patients with glioma, no cases of necrosis were found when the normalized total cumulative dose (NTD_{cum}) was <100 Gy. The NTD_{cum} was the most important factor with regard to the development of radionecrosis. No effect was noticed for the time interval between the initial and reirradiation exposure. In the fractionated stereotactic radiotherapy (FSRT), pathologically confirmed radionecrosis was only seen in series with NTD_{cum} of >105 Gy.[9] Fractionated stereotactic reirradiation was generally performed using a fraction size of >5 Gy, whereas in radiosurgery (SRS), even single dose fraction as high as 18 Gy.

The concise overview of existing salvage strategies, their therapeutic value and associated risk for patients with recurrent malignant glioma was recently presented by Niyazi et al.[14] In the current literature there is no such summary of clinical data on retreatment of children with progressive CNS tumor.

Recently, Merchant et al. described their experience with retreatment of children with recurrent ependymoma. The radiosurgery using median dose of 18 Gy was performed in 6 patients and resulted in significant brain stem toxicity. All children had neuroimaging or pathologic evidence of necrosis. Five of them died. For this reason, in subsequent patients, fractionated reirradiation was performed. This method was demonstrated as better tolerated and giving excellent local control: only 3 of 13 children had disease progression. The conclusion was that high dose single-fraction treatment can be harmful, especially when such a critical structure as the brain stem is involved.[2]

In other reports from Boston Children's Hospital and Heidelberg none of the children with recurrent medulloblastoma had any evidence of late toxicity or radionecrosis after SRS. But the median prescription dose was relatively low, 12 Gy and 15 Gy, respectively.[4,6]

Shaw at al. in the final report of RTOG protocol 90–05 demonstrated that the maximum tumor diameter, the performance status and the tumor dose were associated with the risk of neurotoxicity in the reirradiated patients. The actuarial risk of radionecrosis was 8% and 11% at 1 and 2 years following radiosurgery, respectively. The maximum tolerated doses of single fraction radiosurgery were defined as 24 Gy, 18 Gy and 15 Gy for tumors $\leq$20 mm, 21–30 mm and 31–40 mm in maximum diameter.[15]

Only a few reports have been published on the utility of intraoperative radiotherapy (IORT) in children, especially on its toxicity and efficiency in recurrent brain tumors. Karapurakal et al. described the preliminary results after IORT with a photon radiosurgery system in a group of children with recurrent brain tumors at the first dose level of 10 Gy. The radionecrosis was developed during 6–12 months of follow-up in three children who were not irradiated earlier but had received 10 Gy to a depth of 5 mm. Kalapurkal demonstrated the safety of IORT to a dose of 10 Gy to 2 mm in children previously irradiated.[16]

The promising results were presented by Liu et al. They chose the hypofractionated regimen of reirradiation. All six children given three fractions of 8 Gy are alive with no evidence of disease. In three of them, radionecrosis was suspected based on MRI images, but none of them required significant therapy.[3]

The hypofractionated stereotactic conformal radiotherapy (SCRT) regimen was used by Saran et al. in retreatment of 14 patients with recurrent or residual medulloblastma/PNET. All patients received focal radiotherapy (30–40 Gy/6–8 fractions) using non-coplanar arcs or fixed conformal non-coplanar fields. Median OS was 29 months and median PFS was 12 months. At the time of analysis 8 patients died, all due to progressive disease. In a median time to progression of 12 months, nine recurrences were observed.[5]

Bauman at al. reported the retrospective analysis of 34 patients reirradiated for various CNS tumors between 1977 and 1993. Almost two-thirds of the patients were retreated for the failure located outside the originally treated volume. The patients were reirradiated with the variety of techniques, including hypofractionated, conventionally fractionated and hyperfractionated regimens, for whole or partial brain fields. The median cumulative dose was 79.7 Gy (range: 43.2–111 Gy). The median PFS and OS were 3.3 and 8.3 months, respectively. The repeated treatment was associated with longer median survival in medulloblastoma and meningioma patients: 11.5 and 36.1 months, respectively. This may be the consequence of more indolent behavior of these histologies. The radiological response rate was 58%. The complication rate was 29% (10/34 pts); including 3 patients with brain necrosis.[13]

In our group the median overall survival was 17.5 months, but all children were treated for relatively radiosensitive tumors. The radiological response rate was also better, with 75% of patients showing stable or improved images during the first evaluation. We have not observed late toxicity but in none of the patients the TD_{cum} and BED_{cum} exceeded 100 Gy and 200 Gy, respectively.

Wara et al. after applying the whole brain reirradiation of up to 30 Gy in 10 fractions and giving misonidazol to 28 children with various recurrent brain tumors showed median overall survival and median time to progression of 13 and 5.5 months, respectively. Six patients (21%) developed radiation toxicity and 2 of them died because of this. The whole brain hypofractionated reirradiation schemes should be avoided as they give higher risk of late toxicity.[12]

In Veninga's series of 42 patients over 16 years, the median OS and PFS after reirradiation were 10.9 and 8.6 months. Nearly one-third showed a complete or partial radiological response. Long term complications were seen in 3 patients, all of them received the BED_{cum} of >204 Gy.[7]

Radionecrosis was reported in only one study with hyperfractionated regimen, despite the NTD_{cum} of <90 Gy. This indicates that the repair of sublethal DNA damage is not completed in the 6-h interval between two daily fractions.[9]

The control of craniospinal dissemination remains to be the main problem in treatment of recurrent brain tumors. Repeated radiotherapy could have an important role at preventing local relapse. In Saran's series, the local control rate was 80% at 1 year. The predominant site of failure was distant within the CNS.[5] Similar results were obtained by Milker-Zabel et al. in radiotherapy of recurrent MB. A local tumor progression was seen in three cases of 20 treated children. A multifocal intracranial progression was seen in 9 patients, 5 of them developed additional spinal metastases. Thirteen patients died with disseminated cranio-spinal progression.[4] In our analysis, within the first year after repeated radiotherapy, only 2 of 8 children progressed in the treatment area. At a median follow-up of 16 months, 2 children died from dissemination within the CNS.

All our patients had salvage chemotherapy preceding or/and following reirradiation. Salvage chemotherapy regimens may be recommended as the next modality depending on prior exposure to chemotherapy, anticipated chemosensitivity of the tumor and clinical status of the patient. The combined radio-chemotherapy is likely to increase some side effects, especially with substances with strong radiosensitizing potential.[17] However, the use of chemotherapy was not the significant predictor of toxicity. We included only children reirradiated up to 2009 inclusive to obtain a reliable follow-up time allowing to assess the risk of late damage, including radionecrosis. None of our patients developed any late complications. Four children had mild symptoms of radiotherapy toxicity not requiring medication, the other four had symptoms that required steroids in low doses and/or antiemetic treatment.

6. Conclusion

The fractionated external beam reirradiation with highly conformal three-dimensional planning is certainly an important modality to be considered in the armamentarium for CNS tumor recurrence in children. This report demonstrates that the repeated radiotherapy is not a curative option but could be a therapeutic choice in the absence of other treatment possibilities. This method is intended to consolidate salvage chemotherapy. Reirradiation seems to be effective in inducing a radiological remission for a relevant period of time without acute and late significant sequelae. Patients remained in a satisfactory functional condition at the time of tumor progression. The control of craniospinal dissemination remains to be the main problem. To determine an optimal management strategy in children with recurrent brain tumor, it would be necessary to summarize all single-centre reports of retreatment.

Conflict of Interest

None declared.

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