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Reirradiation of Pediatric Tumors Using Hypofractionated Stereotactic Radiotherapy

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Abstract

Background: This study aimed to evaluate the efficacy and safety of hypofractionated stereotactic radiotherapy for reirradiation of recurrent pediatric tumors. **Methods and Materials:** The study included 23 pediatric patients who were reirradiated using hypofractionated stereotactic radiotherapy in the radiation oncology department between January 2008 and November 2013. In total, 33 tumors were treated—27 (82%) cranial and 6 (18%) extracranial. Hypofractionated stereotactic radiotherapy was administered due to recurrent disease in 31 (94%) tumors and residual disease in 2 (6%) tumors. The median total dose was 25 Gy (range: 15-40 Gy), and the median follow-up was 20 months (range: 2-68 months). **Results:** The 1-year and 2-year local control rates in the entire study population were 42% and 31%, respectively. The median local control time was 11 months (range: 0-54 months) following hypofractionated stereotactic radiotherapy. The patients with tumor response after hypofractionated stereotactic radiotherapy had significantly longer local control than the patients with post-hypofractionated stereotactic radiotherapy tumor progression (21 vs 3 months, $P < .001$). Tumor volume <1.58 cm^3 was correlated (not significantly) with better local control (23 vs 7 months, $P = .064$). **Conclusion:** Reirradiation of pediatric tumors using hypofractionated stereotactic radiotherapy is a safe and effective therapeutic approach. This treatment modality should be considered as a treatment option in selected pediatric patients.

Keywords

pediatric tumors, reirradiation, hypofractionation, stereotactic radiotherapy, stereotactic body radiotherapy

Abbreviations

BED, biological effective dose; CI, conformity index; CT, computerized tomography; CTV, clinical target volume; GTV, gross tumor volume; HFSRT, hypofractionated stereotactic radiotherapy; HI, homogeneity index; LC, local control; OARs, organs at risk; OS, overall survival; RT, radiotherapy

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Introduction

Despite remarkable advancements in cancer treatment, locoregional recurrence remains the predominant cause of death in patients with pediatric cancer.[1] Therapeutic options are often limited and depend on several factors, including patient age, performance status, size, type, and localization of the recurrent tumor, initial treatment modality, and time from initial treatment to recurrence. The goal of retreatment includes palliative intent, prevention of symptoms due to progressive disease, and curative treatment in the absence of metastatic disease.[2]

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In the majority of previously irradiated pediatric patients, salvage surgery and chemotherapy can be used. If patients are not candidates for surgery, reirradiation should be considered. The use of conventional radiotherapy (RT) for reirradiation has been performed in only a few pediatric patients due to the risk of normal tissue toxicity. Reirradiation requires careful consideration of both the overall benefits and indications, as well as the potential late effects, especially in children. Due to the risk of such long-term complications as cognitive and endocrine disorders and the development of secondary cancers, the use of novel RT technology is becoming more popular.

Some recent advancements in RT technology have facilitated precisely directed administration of high-dose radiation focused inside the target volume, while minimizing the radiation dose to surrounding healthy tissues. Hypofractionated stereotactic radiotherapy (HFSRT) has recently been used for the treatment of small tumors with favorable outcomes in many adult tumors.[3-6] Encouraging outcomes in cases of reirradiation of recurrent tumors have also been reported.[2] Many researchers have reported additional radiobiological advantages of HFSRT directed to the tumor microenvironment in addition to intracellular targets. Hypofractionated stereotactic radiotherapy causes endothelial cell damage and a stronger immune response than conventional RT that can increase the therapeutic index.[7-9] Hypofractionated stereotactic radiotherapy is also dosimetrically advantageous because the high dose of radiation to the target volume has a very steep radiation dose falloff beyond the target volume, minimizing collateral damage to surrounding normal tissues, which is especially beneficial in pediatric patients.[10,11]

In adults, HFSRT has been used in many clinical settings, whereas data on the use of this relatively new technology for reirradiation of pediatric tumors are quite limited.[2,12,13] Although most of these studies on HFSRT in pediatric patients included highly selected patient populations or combined previously irradiated and nonirradiated patients, HFSRT might still be considered an option for achieving disease control in confined recurrent pediatric tumors.[12,14-19] Because of the radiobiological and dosimetric advantages of HFSRT, we treated initially irradiated pediatric patients using HFSRT in an attempt to overcome failed initial RT. The aim of this study was to evaluate the efficacy and safety of reirradiation using HFSRT in pediatric patients.

Materials and Methods

Patients

The medical records of all patients aged <19 years who were reirradiated at our radiation oncology department using HFSRT were retrospectively evaluated. All cases were reviewed by the multidisciplinary pediatric tumor board, and alternative treatment modalities for each patient were discussed at the time of presentation. After obtaining informed consent from parents, patients were reirradiated using HFSRT. The protocol for this retrospective study was approved by the ethics committee of Hacettepe University.

Treatment Planning and Delivery

Hypofractionated stereotactic radiotherapy was administered using a CyberKnife (Accuray, Inc, Sunnyvale, California). Patients with cranial tumors were immobilized using a thermoplastic mask. Treatment planning computerized tomography (CT) images were obtained with patients immobilized in the supine treatment position. The gross tumor volume (GTV) and organs at risk (OARs) were delineated on planning CT images. In most cases, the clinical target volume (CTV) was equal to GTV. Planning target volume was determined by adding a mean 1-mm margin around the CTV for intracranial tumors and a mean 2-mm margin for extracranial tumors depending on proximity to critical structures.

Fraction dose and total dose were based on tumor type, proximity to critical structures, and previous RT characteristics. Also cumulative biological effective dose (BED) and time interval between previous RT and reirradiation were considered to limit normal tissue toxicity while maximum effect on the tumor. The conformity index (CI) was defined as the ratio of tissue volume receiving the prescription isodose or more to the tumor volume receiving the prescription isodose or more.[20] The homogeneity index (HI) was defined as the ratio of the maximum dose to the prescription dose.[20] The minimum dose to the target volume and maximum dose to OARs were reported. Following selection of a suitable treatment plan, each patient returned for reirradiation treatment. Before administration of each fraction, all patients were intravenously premedicated with dexamethasone, antiemetic, and an H_2 receptor antagonist. Patients were treated on consecutive weekdays or every other day, according to their treatment plan. If the critical structures received considerable dose, we preferred every other day treatment. Patients ($\leq$6 years of age) were immobilized using general anesthesia.

Follow-Up and Toxicity

Tumor response to treatment was assessed via CT, magnetic resonance imaging, or positron emission tomography/CT 3 months after completion of HFSRT, based on Response Evaluation Criteria in Solid Tumors. Accordingly, tumor disappearance was considered complete response; a >30% decrease in maximum tumor diameter was considered partial response; a >20% increase in tumor size was considered progressive disease; and a $\leq$30% decrease to $\leq$20% increase in tumor size was considered stable disease.

During and after reirradiation, acute and late radiation-induced toxicities were evaluated according to the toxicity criteria of the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer.[21] After HFSRT, all patients were followed up every 3 months during the first 2 years, every 6 months during the next 3 years, and annually thereafter. Complete physical examination, laboratory tests, and diagnostic imaging were performed during all follow-up visits. Follow-up data were obtained from radiation oncology department charts, any available hospital notes, referring

Table 1. Patient, Initial Tumor, and Treatment Characteristics.

Patient No.	Sex	Age at HFSRT	Primary Location	Histology	Prior Treatment
1	F	4	Posterior fossa	Ependymoma	S + C + RT (54 Gy)
2	M	5	Pelvis	Yolk sac tumor	Bx + C + S
3	F	6	Ventricular system	PNET	S + C+ CRT (54/30.6 Gy)
4	M	7	Craniospinal	PNET	Bx + RT (36 Gy)+ C +S
5	F	8	Posterior fossa	Medulloblastoma	S + C + RT (54/30.6 Gy) + SRT
6	M	8	Cheek	RMS	Bx + C + S + RT (50.4 Gy)
7	M	9	Posterior fossa	Medulloblastoma	S + RT (54/36 Gy) + C
8	M	9	Posterior fossa	Medulloblastoma	S + C + RT (54/30.6 Gy)
9	M	9	Posterior fossa	Ependymoma	S + RT (45/36 Gy) + C
10	M	10	Posterior fossa	Medulloblastoma	S + RT (54/30.6 Gy) + C + SRT
11	F	10	Posterior fossa	Medulloblastoma	S + C + RT (54/30.6 Gy)
12	F	11	Craniospinal	Astrocytoma	S + RT (40/34.2 Gy) + C
13	M	11	Systemic disease	Burkitt lymphoma	C
14	M	13	Pineal region	Immature teratoma	S + C + RT (45 Gy)
15	M	13	Posterior fossa	Medulloblastoma	S + RT (54/30.6 Gy) + C
16	F	13	Retro-orbital	Astrocytoma	Bx + RT (50.4 Gy)
17	M	14	Mandibula	Synovial sarcoma	S + RT (60 Gy) + C
18	M	16	Pineal region	Germinoma	Bx + RT (45/23.4 Gy) + C
19	M	16	Basal ganglia	Germinoma	S + RT (50.4/30.6 Gy) + C
20	M	16	Craniospinal	PNET	Bx + C + CRT (54/36 Gy)
21	F	17	Retro-orbital	RMS	S + C + RT (45 Gy)
22	M	17	Cranium	Astrocytoma	Bx + CRT (60 Gy)
23	M	18	Posterior fossa	Medulloblastoma	S + RT (54/31.6 Gy)

Abbreviations: Bx, biopsy; CRT, chemoradiotherapy; C, chemotherapy; F, female; HFSRT, hypofractionated stereotactic radiotherapy; M, male; PNET, primitive neuroectodermal tumor; RMS, rhabdomyosarcoma; RT, radiotherapy; S, surgery; SRT, stereotactic radiotherapy.

doctors, the Turkish General Directorate of Population and Citizenship Affairs, and as a last resort, from parents and/or next of kin.

Statistical Analysis

Statistical analysis was performed using PASW Statistics for Windows v.18.0 (SPSS, Inc, Chicago, Illinois). Local control (LC) was calculated using the Kaplan-Meier method and compared using the log-rank test. Time-related events (treatment failure and mortality) were calculated from the completion of HFSRT to the last follow-up or mortality. Local control was defined as the lack of local progression during follow-up. The effects of patient and treatment variables on LC were assessed using the log-rank test. Tumor type (recurrent or residual), tumor localization (cranial vs extracranial), BED_{3Gy} ($\leq$160 vs >160 Gy), BED_{10Gy} ($\leq$100 vs >100 Gy), treatment schedule (consecutive days vs every other day), number of fractions (1-3 vs 5), time of recurrence ($\leq$2 vs >2 years), time between primary RT and HFSRT ($\leq$20 vs >20 months), and tumor volume (<1.58 vs $\geq$1.58 cm^3) were analyzed. All comparisons were made by taking the median values into consideration. The level of significance was set at $P < .05$.

The total radiation dose was calculated using the standard BED formula ($BED = nd\,[1 + d/\alpha/\beta]$). For acute responding tissues or tumor effects and late responding tissues or normal tissue effects, BED_{10Gy} and BED_{3Gy} were selected, respectively. Median BED_{3Gy} was 88 Gy (range: 47-147 Gy) and median BED_{10Gy} was 38 Gy (range: 28-72 Gy) for HFSRT. Cumulative BED was calculated as the sum of BED for the initial irradiation course and BED for the reirradiation course. Median cumulative BED_{3Gy} was 156 Gy (range: 104-247 Gy) and median cumulative BED_{10Gy} was 101 Gy (range: 70-144 Gy).

Results

Patient, Tumor, and Treatment Characteristics

In total, 23 pediatric patients (7 [30%] females and 16 [70%] males) were reirradiated using HFSRT between January 2008 and November 2013. Median age of the patients was 11 years (range: 4-18 years). Primary diagnoses were medulloblastoma (n = 7), primitive neuroectodermal tumor (n = 3), astrocytoma (n = 3), ependymoma (n = 2), germinoma (n = 2), rhabdomyosarcoma (n = 2), yolk sac tumor (n = 1), Burkitt lymphoma (n = 1), immature teratoma (n = 1), and synovial sarcoma (n = 1).

At the time of initial diagnosis, total resection was performed in 9 (39%) patients and subtotal resection was performed in 8 (35%) patients. The remaining 6 (26%) underwent biopsy. The previous RT site was local in 10 (44%) patients and craniospinal in 13 (56%) patients, and median RT dose was 50.4 Gy (range: 25.2-60 Gy). All patients were previously treated with various chemotherapy protocols in addition to RT. Patient, initial tumor, and treatment characteristics are summarized in Table 1.

In total, 33 tumors were reirradiated—27 (82%) were cranial and 6 (18%) were extracranial. Hypofractionated stereotactic radiotherapy was administered due to recurrent disease in

Table 2. Hypofractionated Stereotactic Radiotherapy Treatment Characteristics.

Patient No.	Site	Tumor Volume, cm^3	Total Dose, Gy/Fraction	BED_{3Gy}	BED_{10Gy}	$cBED_{3Gy}$	$cBED_{10Gy}$
1	Posterior fossa	38.52	25/5	67	38	153	101
2	Pelvis	22.7	30/3	130	60	211	119
3	3rd Ventricle	3.57	30/5	90	48	176	112
4	Spine (T6-T8)	0.58	20/5	47	28	104	70
5	4th Ventricle	1.58	30/5	90	48	133	92
	Left frontal lobe	0.72	18/1	126	50	176	112
	Spine (T10)	3.47	20/5	47	28	212	114
6	Infratemporal fossa	98.1	32.5/5	103	54	184	113
7	Spine	0.26	25/5	67	38	153	101
8	Left lateral ventricle	3.45	30/5	90	48	176	112
	Right occipital horn	2.77	30/5	90	48	176	112
9	Left lateral ventricle	5.29	30/5	90	48	162	101
10	Posterior fossa	0.39	24/3	88	43	174	107
11	4th Ventricle	0.44	25/5	67	38	153	101
	4th Ventricle	0.33	25/5	67	38	153	101
	4th Ventricle	0.31	25/5	67	38	153	101
	4th Ventricle	0.43	25/5	67	38	153	101
	Septum pellucidum	1.58	15/1	90	38	176	101
	Right frontal horn	0.35	15/1	90	38	176	101
12	Cerebellum	19.2	30/6	80	45	153	95
13	Cerebellum	36	24/3	88	43	128	73
14	Pineal region	0.95	25/5	67	38	139	91
15	Spine	1.55	16/2	59	29	139	88
16	Retro-orbital	16.96	25/5	67	38	147	97
17	Masticator space	7.39	40/5	147	72	247	144
18	Left occipital horn	13.5	25/5	67	38	139	91
19	Left occipital horn	0.67	18/1	126	50	207	110
	Left frontal horn	0.11	18/1	126	50	207	110
20	Cerebellum	0.39	18/1	126	50	212	114
21	Retro-orbital	1.77	25/5	67	38	139	91
22	Right parietal lobe	1.66	25/3	94	46	194	118
23	3rd Ventricle	3.35	21/3	70	36	156	99
	Spine (T3-T4)	0.77	21/3	70	36	156	99

Abbreviations: BED, biological effective dose; cBED, cumulative biological effective dose.

31 (94%) tumors and due to residual disease in 2 (6%) tumors. Median target volume was 1.58 cm^3 (range: 0.11-98 cm^3). Median total dose was 25 Gy (range: 15-40 Gy) and normalized to the median 82% isodose line (range: 65%-91%). In all, 13 (39%) tumors were treated using 1 to 3 fractions, and 20 (61%) were treated using 5 fractions. Median CI was 1.43 and the HI was 1.22. Fiducial implantation was required to localize the site of irradiation in 1 (3%) tumor, an X-sight tracking system was used in 5 (15%) tumors, and 27 (82%) tumors were treated using a 6-dimensional skull tracking system. Median total treatment time for each fraction was 45 minutes (range: 18-80 minutes). In total, 18 (54%) tumors were treated on consecutive weekdays and 15 (46%) were treated every other day. Hypofractionated stereotactic radiotherapy treatment details are shown in Table 2. Only 2 (9%) of the patients aged 4 and 5 years required general anesthesia during the procedure.

Overall Survival

Median follow-up after initial diagnosis was 41 months (range: 12-176 months). The 2-year and 5-year overall survival (OS) rates after diagnosis in the entire patient group were 88% and 59%, respectively. Median survival time after initial diagnosis was 65 months. Median follow-up after reirradiation was 20 months (range: 2-68 months). The 2-year and 5-year OS rates after reirradiation in the entire patient group were 60% and 48%, respectively. Among all the patients, median survival time after reirradiation was 28 months.

Local Control

During patient follow-up, recurrence occurred a median of 19 months (range: 1-122 months) after primary RT. Median time from primary RT to reirradiation was 19 months (range: 1-137 months).

At the last follow-up, 11 (48%) patients were alive and 12 (52%) had died due to progressive disease. Initial tumor response 3 months after reirradiation was 73%. Among the treated tumors, there was progression in 9 (27%) tumors, stable appearance in 6 (18%) tumors, partial regression in 8 (24%) tumors, and complete resolution in 10 (31%) tumors. The time from reirradiation to the onset of disease progression was

Table 3. Treatment Characteristics of Recurrence and Final Status of Patients.

Patient No.	Recurrence[a] (at Months FU)	Treatment Course[b]	Response to HFSRT	Local Control,[c] Months	FU, Months	Final Status of Patient/Tx Lesion
1	13	HFSRT	PR	5	12	EX/PD
2	5	C + RT (50.4 Gy) (Rc) + C + HFSRT (Prog) + C	CR	7	21	EX/PD
3	7	HFSRT + C + C (Prog) + C (Prog)	PD	3	7	EX/PD
4	20	HFSRT + C + RT (36 Gy) + C	SD	12	12	AWED/SD
5	0		PR	6	27	EX/PD
	12	HFSRT + C + C (Prog)	CR	23	25	EX/PD
	21	HFSRT + C + C (Prog)	PR	7	13	EX/PD
6	46	C (osteosarcoma) + S + C + S + HFSRT (Rc) + C	PR	10	37	AWED/PD
7	24	S + C + HFSRT	PD	3	13	EX/PD
8	20	HFSRT + C + C (Rc) + C (Prog) + C (Prog)	CR	54	68	AWED/PD
	53	HFSRT + C + C (Rc) + C (Prog) + C (Prog)	CR	29	35	AWED/PD
9	51	S + HFSRT	PD	0	2	EX/PD
10	0		SD	32	32	AWED/SD
11	12	HFSRT + C + C (Prog)	PR	11	20	AWED/PD
	12	HFSRT + C + C (Prog)	PR	11	20	AWED/PD
	12	HFSRT + C + C (Prog)	PR	11	20	AWED/PD
	17	HFSRT + C + C (Prog)	PD	5	20	AWED/PD
	17	HFSRT + C + C (Prog)	PD	5	20	AWED/PD
	17	HFSRT + C + C (Prog)	PD	5	20	AWED/PD
12[d]	28	CRT + C + HFSRT + C	SD	11	14	EX/PD
13	6	C + RT (25.2/21.6 Gy) + C (Rc) + C (Rc) + RT (25 Gy) + HFSRT + C	PD	0	3	EX/PD
14[e]	5	HFSRT + C	CR	29	29	ANED/CR
15	14	HFSRT + C + C (Prog) + C (Prog)	CR	16	16	EX/SD
16	103	S + C + HFSRT	SD	12	12	AWED/SD
17	27	S + HFSRT + C + S (Rc) + S (Rc) + S (Rc) + C	CR	14	25	AWED/PD
18	28	S + C + HFSRT + C	PD	3	12	EX/PD
19	34	C + HFSRT	CR	35	35	ANED/CR
	34	C + HFSRT	CR	35	35	ANED/CR
20	9	HFSRT + C	SD	6	7	EX/PD
21	28	S + C+ HFSRT + C	PR	29	29	AWED/SD
22	1	HFSRT + C	PD	2	8	EX/PD
23	122	C + RT (39.6 Gy) + HFSRT + C	CR	21	35	AWED/PD
	122	C + RT (39.6 Gy) + HFSRT + C	SD	35	35	AWED/SD

Abbreviations: ANED, alive with no evidence of disease; AWED, alive with evidence of disease; CR, complete response; C, chemotherapy; EX, exitus; FU, follow-up; HFSRT, hypofractionated stereotactic radiotherapy; PD, progressive disease; PR, partial response; Prog, progression; Rc, recurrence; RT, radiotherapy; S, surgery; SD, stable disease; Tx, treated.

[a]Duration of time from initial radiotherapy to recurrence.

[b]Treatment course is listed in chronological order, from initial management to last management.

[c]Local control was defined as freedom from local progression after HFSRT.

[d]One month after HFSRT, patient 12 developed grade 1 radiation-induced brain toxicity.

[e]Five months after HFSRT, patient 14 developed grade 3 radiation-induced brain toxicity.

11 months (range: 0-54 months). At the last follow-up, 9 (27%) lesions had LC and tumor progression was noted at the reirradiation site in 24 (73%) lesions. Among the 16 patients with progressive disease, 6 had progression only at the reirradiation site and 10 had local plus additional cranial or craniospinal disease. Among the patients with LC (n = 7), 3 developed systemic disease during follow-up. Treatment modalities for recurrence and final status of the patients are shown in Table 3.

The 1-year and 2-year LC rates in the entire patient group were 42% and 31%, respectively. Median LC time was 11 months (range: 0-54 months) after reirradiation.

Prognostic Factors

There wasn't a significant difference in the 1-year LC rate between the recurrent and residual tumors (42% vs 50%, respectively, $P = .646$). In addition, there weren't any significant differences in 1-year LC according to tumor localization (cranial [41%] vs extracranial [50%], $P = .856$), cumulative BED_{3Gy} ($\leq$160 Gy [41%] vs >160 Gy [44%], $P = .929$), cumulative BED_{10Gy} ($\leq$100 Gy [64%] vs >100 Gy [32%], $P = .196$), treatment schedule (consecutive days [44%] vs every other day [40%], $P = .727$), number of fractions (1-3 [54%] vs 5 [35%], $P = .586$), or the time between primary RT and HFSRT ($\leq$20 months [44%] vs >20 months [60%], $P = .122$). The

1-year LC rate was 26% and 64%, respectively, when recurrence time was ≤2 years and >2 years ($P = .121$). Patients who had tumor response after reirradiation had significantly longer LC than patients with tumor progression (21 vs 3 months, $P < .001$). Similarly, median LC time in patients with complete response, partial response, stable disease, and progressive disease was 29, 10, 35, and 3 months, respectively ($P < .001$). Tumor volume <1.58 cm^3 was correlated (not significantly) with better LC (23 vs 7 months, $P = .064$).

Toxicity

Treatment was delivered as planned in all patients, and treatment tolerability was excellent. In all, 2 (9%) patients (patients 12 and 14 in Table 3) developed radiation-induced brain toxicity 1 and 5 months after reirradiation, respectively. Patient 14 had clinical and radiological signs of brain necrosis (grade 3), whereas patient 12 only had radiological signs of brain necrosis (grade 1); gabapentin was prescribed for patient 14 and steroid treatment for patient 12. Both patients had complete response to these treatments and had problem-free recovery. There weren't any cases of mortality due to treatment-related complications.

Discussion

Therapeutic options for recurrent tumors in previously irradiated children are limited. Most pediatric patients are not candidates for resurgery, and salvage chemotherapy provides only a palliative effect. Reirradiation can result in temporary LC, but unfortunately, only a small number of patients undergo reirradiation due to the risk of normal tissue toxicity.

The literature primary includes reports on the drawbacks of reirradiation in pediatric patients, whereas its benefits are not fully known and there is a lack of specific guidelines for its use. Only a few studies have reported on pediatric patients with recurrent tumors treated using reirradiation.[22,23] Additionally, most of the relevant studies included both adult and pediatric patients with various types of tumors.[23,24] The present study's patient population was not homogeneous in terms of primary diagnosis, tumor localization, or initial treatment modality. As each type of tumor in the present study was present in only a few patients, it is difficult to reach a definitive conclusion about the response rate to reirradiation using HFSRT for each type of tumor.

According to the literature, the role of single-fraction stereotactic radiotherapy in the treatment of recurrent tumors is controversial.[11,25] Generally, the HFSRT-related complication rate is high and the long-term disease control rate is low.[11,19,25] Merchant *et al* reported a series of 6 pediatric patients who underwent a second course of RT for recurrent ependymoma.[19] Reirradiation included radiosurgery (n = 6), focal fractionated reirradiation (n = 13), or craniospinal irradiation (n = 19). All of their patients were treated with a median dose of 18 Gy radiosurgery, which resulted in high-grade brain stem toxicity. Due to the high rate of toxicity-related mortality (5 of 6 patients died), subsequent patients underwent fractionated reirradiation. They suggested that an excellent rate of disease control and a better toxicity profile were obtained with fractionated reirradiation for recurrent ependymomas. Studies conducted at Boston Children's Hospital and Heidelberg reported that none of the children with recurrent medulloblastoma had late toxicity after radiosurgery with a median dose of 12 and 15 Gy, respectively.[23,26]

Although promising results have been achieved with reirradiation, toxicity remains a major problem. Even with HFSRT, some OARs are irradiated. Radiation damage is dependent on the type and localization of tissue exposed to radiation, total dose, fractionation regimen, and time from previous RT.[27] Children are more sensitive to radiation than adults.[28] Other risk factors are use of chemotherapy, a low CI, short overall treatment time, and diabetes mellitus.[29] Long-term complications of reirradiation were observed in patients with recurrent brain tumors who received a cumulative dose >204 Gy BED.[30] Padovani *et al* treated 7 children with recurrent medulloblastoma using 3-dimensional conformal reirradiation and reported that no neurological toxicity was observed when a median cumulative BED2 of 168 Gy was used.[31] Shaw *et al* reported that the risk of neurotoxicity is associated with maximum tumor diameter, performance status, and total dose in adult patients reirradiated using radiosurgery.[32] Although the median cumulative BED_{3Gy} was 156 Gy (range: 104-247 Gy) in the present study, long-term serious toxicity associated with this high cumulative dose of radiation was not observed. Only 2 of the present study's patients had brain necrosis following a cumulative BED_{3Gy} of 139 Gy (n = 1) and 153 Gy (n = 1). Both of these patients were fully recovered clinically and radiologically at the last follow-up; however, median follow-up time was only 20 months in the present study, and longer term follow-up is required to observe late toxicity and secondary malignancies.

Chojnacka *et al* analyzed reirradiation outcomes in 8 pediatric patients with recurrent brain tumors.[33] Initially, all of their patients were treated with surgery, chemotherapy, and RT. Three-dimensional image-based conformal RT for reirradiation was used at a median RT dose of 40 Gy in 2 Gy daily fractions. Their median cumulative BED was 144 Gy (range: 126-181 Gy), and their median OS and progression-free survival were 17.5 and 6.5 months, respectively. Reirradiation was well tolerated, and none of their patients exhibited late toxicity. Based on these findings, we think that in children with recurrent brain tumors, fractionated reirradiation with highly conformal 3-dimensional RT should be considered a viable treatment option.

Bouffet *et al* reported 47 pediatric patients with relapsed ependymoma who were treated with surgery and/or chemotherapy (n = 29) and full-dose reirradiation with or without surgery (n = 18)[12]. They reported that 3-year OS was 7% ± 6% and 81% ± 12% for non-reirradiated and reirradiated patients, respectively ($P < .0001$). Only 2 of their patients were treated with radiosurgery; however, fractionated RT was given to all the other patients using intensity-modulated RT and daily

cone-beam image guidance RT. The RT dose for recurrence was 59.4 Gy in 33 fractions or 54 Gy in 30 fractions in their patients who had previously received 54 or 59.4 Gy, respectively. No severe acute complications were observed after reirradiation. In 18 of their patients with a mean follow-up of 3.73 years, only 2 had endocrine dysfunction and 1 required special education support. Whereas, it was noticed that intellectual function from pre- to post-reirradiation assessment was decreased.

Due to the present study's small heterogeneous patient population and limited follow-up, it is difficult to delineate the precise role of HFSRT; however, the present findings show that HFSRT might be an effective treatment option for selected pediatric patients with recurrent tumors. The present findings show that reirradiation using HFSRT for pediatric tumors previously treated using RT is safe; however, local recurrence was a major problem. Future studies based on a similar treatment protocol should examine use of higher doses. Following reirradiation, pediatric patients should be followed up closely due to the risk of late recurrence, potential side effects, and radiation-induced malignancies. Additional prospective studies with longer follow-up periods are warranted to gain a better understanding of the long-term effectiveness and toxicity associated with HFSRT for reirradiation of recurrent pediatric tumors.

Authors' Note

This work is original and has not been accepted for publication nor is concurrently under consideration elsewhere and will not be published elsewhere without the permission of the editor. All the authors contribute directly to the planning, execution, and/or analysis of the work reported herein and/or to manuscript preparation.

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References

1. Tomlinson FH, Scheithauer BW, Meyer FB, et al. Medulloblastoma: I. Clinical, diagnostic, and therapeutic overview. *J Child Neurol*. 1992;7(2):142-155.
2. Mantel F, Flentje M, Guckenberger M. Stereotactic body radiation therapy in the re-irradiation situation—a review. *Radiat Oncol*. 2013;8:7. doi:10.1186/1748-717X-8-7.
3. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA*. 2010; 303(11):1070-1076. doi:10.1001/jama.2010.261.
4. Lagerwaard FJ, Haasbeek CJ, Smit EF, Slotman BJ, Senan S. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2008;70(3):685-692. doi:10.1016/j.ijrobp.2007.10.053.
5. Choi BO, Jang HS, Kang KM, et al. Fractionated stereotactic radiotherapy in patients with primary hepatocellular carcinoma. *Jpn J Clin Oncol*. 2006;36(3):154-158.
6. King CR, Brooks JD, Gill H, Presti JC Jr. Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate cancer. *Int J Radiat Oncol Biol Phys*. 2012;82(2): 877-882. doi:10.1016/j.ijrobp.2010.11.054.
7. Fuks Z, Kolesnick R. Engaging the vascular component of the tumor response. *Cancer Cell*. 2005;8(2):89-91.
8. Garcia-Barros M, Paris F, Cordon-Cardo C, et al. Tumor response to radiotherapy regulated by endothelial cell apoptosis. *Science*. 2003;300(5622):1155-1159.
9. Milano MT, Constine LS, Okunieff P. Normal tissue toxicity after small field hypofractionated stereotactic body radiation. *Radiat Oncol*. 2008;3:36. doi:10.1186/1748-717X-3-36.
10. Lo SS, Chang EL, Suh JH. Stereotactic radiosurgery with and without whole-brain radiotherapy for newly diagnosed brain metastases. *Expert Rev Neurother*. 2005;5(4):487-495.
11. Lo SS, Chang EL, Sloan AE. Role of stereotactic radiosurgery and fractionated stereotactic radiotherapy in the management of intracranial ependymoma. *Expert Rev Neurother*. 2006;6(4): 501-507.
12. Bouffet E, Hawkins CE, Ballourah W, et al. Survival benefit for pediatric patients with recurrent ependymoma treated with reirradiation. *Int J Radiat Oncol Biol Phys*. 2012;83(5):1541-1548. doi: 10.1016/j.ijrobp.2011.10.039.
13. Calcerrada Díaz-Santos N, Blasco Amaro JA, Cardiel GA, Andradas Aragonés E. The safety and efficacy of robotic image-guided radiosurgery system treatment for intra- and extracranial lesions: a systematic review of the literature. *Radiother Oncol*. 2008; 89(3):245-253. doi:10.1016/j.radonc.2008.07.022.
14. Zacharoulis S, Ashley S, Moreno L, Gentet JC, Massimino M, Frappaz D. Treatment and outcome of children with relapsed ependymoma: a multi-institutional retrospective analysis. *Childs Nerv Syst*. 2010;26(7):905-911. doi:10.1007/s00381-009-1067-4.
15. Messahel B, Ashley S, Saran F, et al; Children's Cancer Leukaemia Group Brain Tumour Committee. Relapsed intracranial ependymoma in children in the UK: patterns of relapse, survival and therapeutic outcome. *Eur J Cancer*. 2009;45(10):1815-1823. doi: 10.1016/j.ejca.2009.03.018.
16. Liu AK, Foreman NK, Gaspar LE, Trinidad E, Handler MH. Maximally safe resection followed by hypofractionated re-irradiation for locally recurrent ependymoma in children. *Pediatr Blood Cancer*. 2009;52(7):804-807. doi:10.1002/pbc.21982
17. Kano H, Yang HC, Kondziolka D, et al. Stereotactic radiosurgery for pediatric recurrent intracranial ependymomas. *J Neurosurg Pediatr*. 2010;6(5):417-423. doi:10.3171/2010.8.PEDS10252.
18. Krieger MD, McComb JG. The role of stereotactic radiotherapy in the management of ependymomas. *Childs Nerv Syst*. 2009; 25(10):1269-1273. doi:10.1007/s00381-009-0879-6.
19. Merchant TE, Boop FA, Kun LE, Sanford RA. A retrospective study of surgery and reirradiation for recurrent ependymoma. *Int J Radiat Oncol Biol Phys*. 2008;71(1):87-97. doi:10.1016/j.ijrobp.2007.09.037.

20. Shaw E, Kline R, Gillin M, et al. Radiation therapy oncology group: radiosurgery quality assurance guidelines. *Int J Radiat Oncol Biol Phys*. 1993;27(5):1231-1239.
21. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys*. 1995;31(5):1341-1346.
22. Abe M, Tokumaru S, Tabuchi K, Kida Y, Takagi M, Imamura J. Stereotactic radiation therapy with chemotherapy in the management of recurrent medulloblastomas. *Pediatr Neurosurg*. 2006; 42(2):81-88.
23. Milker-Zabel S, Zabel A, Thilmann C, et al. Results of three-dimensional stereotactically-guided radiotherapy in recurrent medulloblastoma. *J Neurooncol*. 2002;60(3):227-233.
24. Bauman GS, Sneed PK, Wara WM, et al. Reirradiation of primary CNS tumors. *Int J Radiat Oncol Biol Phys*. 1996;36(2):433-441.
25. Weprin BE, Hall WA, Cho KH, Sperduto PW, Gerbi BJ, Moertel C. Stereotactic radiosurgery in pediatric patients. *Pediatr Neurol*. 1996;15(3):193-199.
26. Patrice SJ, Tarbell NJ, Goumnerova LC, Shrieve DC, Black PM, Loeffler JS. Results of radiosurgery in the management of recurrent and residual medulloblastoma. *Pediatr Neurosurg*. 1995; 22(4):197-203.
27. Schultheiss TE, Kun LE, Ang KK, Stephens LC. Radiation response of the central nervous system. *Int J Radiat Oncol Biol Phys*. 1995;31(5):1093-1112.
28. Kleinerman RA. Cancer risks following diagnostic and therapeutic radiation exposure in children. *Pediatr Radiol*. 2006;36(suppl 2):121-125.
29. Lawrence YR, Li XA, el Naqa I, et al. Radiation dose-volume effects in the brain. *Int J Radiat Oncol Biol Phys*. 2010;76(3 suppl):s20-s27. doi:10.1016/j.ijrobp.2009.02.091.
30. Veninga T, Langendijk HA, Slotman BJ, et al. Reirradiation of primary brain tumours: survival, clinical response and prognostic factors. *Radiother Oncol*. 2001;59(2):127-137.
31. Padovani L, Andre N, Gentet JC, et al. Reirradiation and concomitant metronomic temozolomide: an efficient combination for local control in medulloblastoma disease? *J Pediatr Hematol Oncol*. 2011;33(8):600-604. doi:10.1097/MPH.0b013e3182331eaf.
32. Shaw E, Scott C, Souhami L, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. *Int J Radiat Oncol Biol Phys*. 2000;47(2):291-298.
33. Chojnacka M, Skowrońska-Gardas A, Pędziwiatr K, Morawska-Kaczyńska M, Perek M, Perek D. Reirradiation of relapsed brain tumors in children. *Rep Pract Oncol Radiother*. 2011;17(1):32-37.