Craniospinal Irradiation As Part of Re-Irradiation for Children With Recurrent Medulloblastoma.

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Abstract

Background

Many studies have demonstrated in the last years that once medulloblastoma has recurred, the probability of regaining tumor control is poor despite salvage therapy. Although re-irradiation has an emerging role in other relapsed brain tumors, there is a lack of strong data on re-irradiation for medulloblastoma.

Methods

This is a retrospective cohort study of patients aged 18 years or under, treated at least by a second course of external beam for recurrence medulloblastoma at Garrahan Hospital between 2009 and 2020. Twenty-four patients met eligibility criteria for inclusion. All patients received upfront radiotherapy as part of the curative-intent first radiotherapy, either craniospinal irradiation (CSI) followed by posterior fossa boost in 20 patients or focal posterior fossa radiation in 4 infants. The second course of radiation consisted of CSI in 15 and focal in 9. The 3-year post first failure OS (50% vs. 0%; p = 0.0010) was significantly better for children who received re-CSI compared to children who received focal re-irradiation. Similarly, the 3-year post-re-RT PFS (31% vs. 0%; p = 0.0005) and OS (25% vs. 0%; p = 0.0003) was significantly improved for patients who received re-CSI compared to patients who received focal re-irradiation. No symptomatic intratumoral haemorrhagic events or symptomatic radionecrosis were observed. Survivors fell within mild to moderate intellectual disability range, with a median IQ at last assessment of 58 (range 43–69).

Conclusion

Re-irradiation with CSI is a safe and effective treatment for children with relapsed medulloblastoma; improves disease control and survival compared with focal re-irradiation. However this approach carries a high neurocognitive cost.

Introduction

Historically, medulloblastoma relapse has been associated with a 2-year post-recurrence overall survival of approximately 25% (1, 2). Many studies have demonstrated in the last years that once medulloblastoma has recurred, the probability of regaining tumor control is poor despite salvage therapy (3). The optimal approach to treating relapsed medulloblastoma remains in doubt and may include repeat surgery, systemic therapy, high dose chemotherapy with stem cell rescue, oral palliative chemotherapy, low intensity multiagent chemotherapy combinations with antiangiogenic effect and re-irradiation (4–6).

Although re-irradiation has an emerging role as a palliative treatment for children with recurrence high-grade glioma, relapse ependymoma and progressive brainstem glioma, there is a lack of strong data on re-irradiation for medulloblastoma (7–9). While radiation therapy is an essential component of multimodality therapy in the treatment of newly diagnosed medulloblastoma, there has been much debate about the use of irradiation at the time of progression because of the potential toxicity and uncertainty about its ability to improve overall survival. Although some recovery of organs at risk occurs over time (10), re-irradiation is challenging in medulloblastoma and often eluded due to a desire to avoid exceeding radiation tolerances and concern over late treatment toxicities (11). Previously, the study from St. Jude Children's Research Hospital suggested that undergoing a second course of radiation may have contributed to better overall survival in patients with recurrent medulloblastoma and may be considered a reasonable salvage treatment option in selected patients who have minimal residual disease at the time of recurrence (12). Furthermore, Sick Children Hospital experience showed that re-irradiation can offer some patients disease control, particularly those with focally recurrent disease in the brain but poor outcome in symptomatic recurrence or disseminated disease (13). Recently, Gupta et al provided encouraging survival outcomes with acceptable toxicity in selected recurrent medulloblastoma treated by re-irradiation as part of multimodality salvage therapy (14).

Craniospinal irradiation (CSI) as a component of re-irradiation was previously reported in small series (12, 13, 14). Recently, the Sick Children group suggested that CSI could be considered one of the treatment tools to help with distant tumor control, considering the very high incidence of distant failures after focal re-irradiation (13). Moreover, Gupta et al suggested that recurrence medulloblastoma with leptomeningeal dissemination could be benefited by re-CSI (14). However, this aggressive salvage strategy must be approached cautiously and further studies are needed to understand the correct balance between toxicity and re-irradiation benefit.

In this study we evaluate the impact of irradiation on overall survival as a component of a salvage therapy for recurrent medulloblastoma, the toxicity of re-irradiation, and the pattern of relapse after a second course of radiation.

Methods

This is a retrospective cohort study of patients aged 18 years or under, treated at least by a second course of external beam radiotherapy for recurrence medulloblastoma at Garrahan Hospital between June 2009 and May 2020. Patients who received re-irradiation for a reason other than recurrent medulloblastoma (i.e. second neoplasm of a different histology) were excluded. Clinicopathologic variables were recorded, including: age at first and second course of irradiation, surgical details, histopathology, radiation dose and fields, acute and late toxicities due to radiotherapy, patterns of relapse after first and second course of irradiation, and vital status. The study was approved by the research ethics boards of Garrahan Hospital.

Treatment

All radiation treatments were given at Garrahan Hospital, Buenos Aires, Argentina. Photon external beam therapy was used for all patients. All but four patients received CSI as part of the first radiation course (RT1), followed by a boost to the entire posterior fossa. Standard risk (SR) patients received CSI 23.4Gy followed by posterior fossa boost 30.6Gy and high-risk (HR) patients received CSI 36Gy followed by posterior fossa boost 19.8Gy. Except for one, all of them received maintenance platinum based chemotherapy; SR as per ACNS0331 (N=2) and COG 9961 (regimen A=3, regimen B= 6); HR as per ACNS0332 (Regimen A=4, Regimen B=4). Four patients received upfront posterior fossa radiotherapy (54 Gy) due to the young age at diagnosis as per standard of care treatment administered between 2002 and 2020 at Hospital Garrahan, based on a modified POG-9934 strategy (15).

Upon recurrence, most patients with brain solitary lesions were offered surgery followed by metronomic chemotherapy and a second course of irradiation (RT2), while those with multifocal disease received chemotherapy followed by radiotherapy. CSI was administered using standard beam's eye-view treatment planning techniques. Boost treatment and focal radiotherapy was administered using 3D-conformal radiation therapy methods. Hypofractionated stereotactic radiotherapy was used in 1 patient. Conventional fractionation (1.8 Gy) was used in all CSI cases, including RT2-RT3 prescriptions. The re-irradiation field and dose, and the irradiation time after recurrence were not systematic and were based on performance status, tumor extension, dose and field at RT1, time between RT1 and RT2, social environment and radiation therapist consideration. The four infants who received upfront posterior fossa radiotherapy, were offered CSI with boost in the recurrence field at relapsed.

Analysis

RT1 was defined as the first radiation course used at diagnosis as part of the curative-intent first treatment, RT2 as the second course of radiation after recurrence and RT3 as a third course of radiation after recurrence. Time intervals between treatments were counted from the first day of RT1 or RT2-RT3. The Kaplan–Meier method was used to calculate progression free survival (PFS) and overall survival (OS) from diagnosis, date of recurrence and the first day of RT2/RT3 (RT3 was considered in the cases with three radiation courses). The differences in outcome between patients groups were tested using the Log Rank method. Associations between different categorical variables were investigated by Fisher's exact test. Survival analysis of those patients who did not receive CSI upfront (as part of RT1) were described separately.

Results

Twenty-four patients met eligibility criteria for inclusion. The list of all patients with medulloblastoma treated with two or more courses of radiotherapy is summarized in table 1. All patients received upfront radiotherapy as part of the curative-intent first radiotherapy, either craniospinal radiotherapy followed by posterior fossa boost in 20 patients (12 SR and 8 HR) or focal posterior fossa radiation in 4 infants. Re-irradiation timing per risk is described in table 2. Two patients received a third course of radiation at 3.4 and 1.8 years after RT2 (SR=1, HR=1). Except for 2, all patients received additional treatment after RT2 as low dose chemotherapy, anti VEGF or multiagent chemotherapy combination with antiangiogenic effect.

The re-irradiation followed surgery and/or chemotherapy in 20 patients. The four patients who were treated by radiotherapy immediately after recurrence, 3 had an isolated spinal cord relapse and 1 an isolated ST lesion (infant=3 and HR=1). Among the 9 patients (SR=5, HR=3, Infant=1) first treated with surgery (biopsy=1, STR=4, GTR=4), 3 (HR) patients with isolated recurrence (ST=2, SC=1) did not received chemotherapy prior to RT2. Among the 15 patients who did not undergo surgery at time of relapse, 11 received chemotherapy prior to RT2. The second course of radiation consisted of CSI in 15 (infant=4, SR=7, HR=4) and focal in 9 (SR=5, HR=4). One patient did not complete the focal re-irradiation course due to a disseminated systemic infection by herpes zoster.

Twelve patients received 2 courses of CSI as part of RT1 and RT2 or RT3. The dose of CSI at RT2/RT3 for SR and HR was 21.6Gy, except for one patient (SR) who received 19.8Gy. The median time between two courses of CSI (RT1-RT2 or RT1-RT3) was 3.3 years (range 0.7-5 years), while the median time between CSI and focal radiotherapy was 2.2 years (range 1-4.8 years). The median cumulative maximum dose applied to the spinal cord for the subgroup who received two courses of CSI was 52.2Gy (range 43.2-59.4), being 45Gy for SR and 57.6 for the HR. Radiotherapy details are described in table 3 and supplementary table 1.

The overall PFS rates for the SR and HR group were 28% at 3 years and 0% at 5 years compared with the OS rates at 3 years of 80% and 35% at 5 years (Figure 1, a). The 3-year post-initial failure OS was 58% for the subgroup who received 2 courses of CSI while 0% for the subgroup with focal re-irradiation (p=0.001 HR 0.1082 95% CI [0.02867-0.4085]) (Figure 1, b). Median OS from RT2 for patients who received 2 courses of CSI was 19.3 months, while patients who received a focal RT2 was 5 months. The 3-year post-re-RT PFS (31% vs. 0%; p=0.0005 HR 0.0938 95% CI [0.02476-0.3561]) and OS (25% vs. 0%; p=0.0003 HR 0.0792 95% CI [0.02023-0.3104]) were significantly improved for patients who received CSI as RT2 compared to patients who received focal re-irradiation (Figure 1, c and d). Cumulative radiotherapy dose and overall survival correlation are described in table 3. Survival outcome is summarized in supplementary table 2. Apart from re-CSI, no other statistically significant predictor of survival improvement was identified including risk at diagnosis, IV topotecan, chemotherapy prior to RT2 or anti VEGF. Moreover, surgery at relapse did not offer an overall survival benefit in the present study (p=0,52) (Supplementary table 3).

All 4 infants medulloblastoma were excluded from above survival analysis considering the difference between upfront radiation field (focal vs. CSI) and the distinctive biology. Median time of survival from diagnosis was 6.15 years. Median OS from recurrence for the infant subgroup was 4.35 years while the median OS from RT2 was 3.45 years. The 3-year post-initial failure OS was 100% while 3-year post-re-RT PFS and OS were 66%.

At the time of the analysis, 6 patients were alive; 5 (infant=2, HR=3) with no evidence of disease and 1 with tumor progression (SR). All of them had received CSI as part of RT2/RT3. The median follow-up for the alive patients was 7 years (range 5.5-11.2). Details of the survivors are included in supplemental table 5

Toxicity

Toxicities were identified through a retrospective chart review. No patients discontinued therapy due to adverse effects suggesting acceptable tolerability. Haematology toxicities without transfusion requirement were observed in 3 patients who received CSI as RT2 (infant=1, SR=1, HR=1); CTCAE version 4.03, grade 2 and grade 3. Other toxicities included asymptomatic hypothyroidism in 5 patients diagnosed after the second course of radiation. No other adverse events were reported, specifically no symptomatic intratumoral haemorrhagic events or symptomatic radionecrosis were observed in our cohort. None of them required hospitalization during the re-irradiation period. Three asymptomatic radionecrosis were found at 3 and 6 months after RT2. Only 1 patient received a high dose of dexamethasone at the time of initial RT2 and was able to taper it upon 2 weeks of initiation of therapy.

Assessment of intellectual functioning

Assessment of neurocognitive outcome was performed in the 6 alive patients with a median time from RT1 of 6.26 years (range 4.45-10.13) and from RT2 of 4.22 (range 0.49-6.7). All the survivors fell within mild to moderate intellectual disability range in the Wechsler Intelligence Scale, with a median IQ at last assessment of 58 (range 43-69) (Figure 2 and supplementary table 4).

Discussion

Herein we describe to our knowledge the largest pediatric cohort reported to date of external beam re-irradiation for children with recurrent medulloblastoma, including toxicity description and neurocognitive analysis. Furthermore, we compare CSI vs. focal radiotherapy as RT2/RT3 in combinations with novel therapies.

CSI as a component of re-irradiation was reported previously by Bakst et al. (one patient), Wetmore et al. (eight SR patients) and Gupta et al. (seven patients) (16, 12, 14). Previously, Wetmore et al. from St. Jude Children's Research Hospital showed a median survival of 5.4 years in 11 re-irradiated standard risk relapsed medulloblastoma (eight of them had received repeat CSI) suggesting that a second course of radiotherapy may have contributed to better OS in patients with recurrent medulloblastoma (12). Although Tsang et al. were unable to evaluate the role of repeat CSI, the very high incidence of distant failures amongst their 14 patients treated with focal re-irradiation, suggested that CSI may be one of the treatment tools of distant disease control (13). Our study showed an OS advantage of re-irradiation as part of a multiagent approach over the history reports, with significantly better outcome in the CSI subgroup. Interestingly, none of the previous studies of salvage re-irradiation in recurrent medulloblastoma had sufficient data to assess the real impact of CSI vs. focal re-irradiation on post-progression outcomes. Moreover, the results of our study appear quite promising and provide evidence of efficacy as well as confirm the safety of re-CSI in the salvage setting, showing a significant difference in the post-re-RT PFS and OS between re-CSI vs. focal radiotherapy. On the other hand, relapsed infant medulloblastoma also seems to be benefited by re-CSI displaying prolonged survival after first recurrence and RT2.

In this study, the cumulative physical dose to organs at risk (OARs) was calculated adding the RT1 dose (reduced by 80% regarding the neuronal tissues capacity for recovery over the years (17–18) to the RT2 prescribed dose. Cumulative OARs doses exceeded the QUANTEC dose constraints; however this was accepted considering the limited life expectancy of this group of patients. Except for one, all patients completed the prescribed course of radiotherapy and none of them developed radiation necrosis or hemorrhagic events. On the other hand, the formal neuropsychological testing performed after re-irradiation in the survivors subgroup, shows that this approach does carry a significant risk to long-term neurocognitive outcomes; significantly below the population mean, constituting a mild-moderate intellectual disability. Moreover, further cognitive deterioration is expected considering the cognitive assessment was performed at a median time of less than 5 years from RT2. One limitation of our analysis is the likely bias toward formal neuropsychological testing only in survivors and the lack of baseline neurocognitive assessment prior to RT2 in all survivors, which will need to be addressed in future prospective studies. As such, any further attempts to incorporate re-irradiation into the management of recurrence medulloblastoma, particularly group 4 and infant subgroup (likely to be rescued), will need to carefully determine the risk ratio of neurocognitive damage from the second radiotherapy course versus the expected progressive neurocognitive decline over the years after RT1.

Previous studies suggested that administration of metronomic chemotherapy (refers to the chronic administration of chemotherapeutic agents at relatively low dose without prolonged drug-free breaks) modulate anti-tumoral immunity and induce tumor dormancy (19). Different combination therapies such as oral TMZ and etoposide were suggested to be effective against recurrent medulloblastoma in a limited cohort (20). On the other hand, multidrug-antiangiogenic therapy consisting of a five-drug oral regimen with anti VEGF plus intrathecal therapy was shown to be beneficial in a small series of relapsed medulloblastoma (21). In our series, a multiagent approach has been implemented, combining re-irradiation with novel therapies, showing impressive survival benefits in a large pediatric recurrence medulloblastoma cohort. Moreover, the relatively high numbers of patients included in our study suggest a feasible approach in the daily clinic.

The major limitations of this study are the retrospective design, the relatively small sample size and the lack of successful molecular subgroup characterization (n = 4). Prospective multicentre longitudinal studies of recurrent medulloblastoma in a subgroup specific manner are required to determine if re-irradiation (CSI vs. local) confers more benefit in particular subgroups, considering the significant differences with respect to the anatomical and temporal patterns of recurrence across subgroups. Recently, a difference in post-progression outcomes between two molecular medulloblastoma subgroups (SHH vs. Group 4) treated by multi-modality salvage therapy (including radiotherapy) was described (14). On the other hand, time to death post-recurrence could be influenced by molecular subgroups having the potential to bias results (22).

Another important consideration is that radiotherapy was not used in a systematic approach and was implemented in combination with other therapies modalities such as surgery, metronomic chemotherapy, anti VEGF and intraventricular topotecan; representing considerable confounding factors and limitations in the statistical interpretation results.

In a pediatric recurrent medulloblastoma cohort, a statistically significant PFS and OS benefit was observed with CSI as a component of re-irradiation, compared with those treated with focal RT2. However, our encouraging findings need to be interpreted cautiously given the inherent biases of the study and

warrant further prospective systematic investigation in larger molecularly defined cohorts. Until these data become available, patients with recurrent medulloblastoma could be offered the option of repeat CSI as part of re-irradiation to maximize the likelihood of disease control, though the potential benefits should be weighed against the long-term side effects of re-CSI. It appears clear however, that the vast majority of relapsed patients cannot be cured, therefore re-CSI plays a palliative care role in most of them and new drugs in early phase trials are urgently needed.

Declarations

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Code availability: Not applicable

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Importance of the study: Our study provides a framework for efficacy and safety of craniospinal re-irradiation to treat relapsed medulloblastoma. This approach does carry a significant risk to long-term neurocognitive outcomes; significantly below the population mean.

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Tables

Table 1
List of all patients with medulloblastoma treated with two or more courses of radiotherapy.

ID	Risk at diagnosis	Diagnosis Metastatic status	Pathology	1st surgery	RT1 Volume	Initial pattern of failure after RT1	Surgery at 1st relapse	Chemo prior to RT2	RT2 Volume	Chemother RT2
1	Standard	M0	Desmoplastic	GTR	CSI, PF	ST	STR	IV Topotecan,Temozolomide,VP16	CSI, boost	Anti VEGF
2	Standard	M0	Classic	GTR	CSI, PF	Ventricle	None	Temozolomide,VP16	CSI, boost	Anti VEGF
3	Standard	M0	Desmoplastic	GTR	CSI, PF	Ventricle	GTR	IV Topotecan,Temozolomide,VP16	CSI, boost	Anti VEGF
4	Standard	M0	Classic	GTR	CSI, PF	Ventricle/PF	None	IV Topotecan,Temozolomide,VP16	Focal	Anti VEGF, Topotecan
5	Infant	M0	Classic	GTR	PF	Ventricle	GTR	IV Topotecan,Temozolomide,VP16	CSI	Anti VEGF
6	Standard	M0	Desmoplastic	GTR	CSI, PF	LS	None	IV Topotecan,Temozolomide,VP16	CSI, boost	Anti VEGF
7	Standard	M0	Classic	GTR	CSI, PF	ST	GTR	IV Topotecan,Temozolomide,VP16	HFSRT	Anti VEGF
8	**High**	**M2**	**Desmoplastic**	**STR**	**CSI, PF**	**Ventricle**	**None**	**IV Topotecan, Temozolomide,VP16**	**CSI, boost**	**5D, IV Topo**
9	Standard	M0	Classic	GTR	CSI, PF	Ventricle, multiple SC	None	Temozolomide,VP16	CSI, boost	Temozolor
10	**High**	**M2**	**Classic**	**GTR**	**CSI, PF**	**ST**	**None**	**Temozolomide,VP16**	**CSI, boost**	**Temozolor**
11	High	M0	Anaplastic	GTR	CSI, PF	Isolated SC	STR	None	Focal	5D, IV Topo
12	**Infant**	**M0**	**Classic**	**GTR**	**PF**	**Isolated SC**	**None**	**None**	**CSI, boost**	**5D, IV Topo**
13	High	M2	Classic	STR	CSI, PF	ST	None	5D, IV Topotecan	CSI, boost	CCNU, Temozolor
14	Infant	M1	Classic	STR	PF	ST	None	None	CSI, boost	5D, IV Topo
15	**High**	**N/A**	**Desmoplastic**	**GTR**	**CSI, PF**	**Isolated SC**	**None**	**None**	**Focal**	**Cyclophosp VCR, Cispla IV Topotec**
16	**Standard**	**M0**	**Desmoplastic**	**GTR**	**CSI, PF**	**Multiple SC**	**None**	**5D, IV Topotecan /CCNU-Temozolomide**	**CSI, boost**	**None**
17	Standard	M0	Classic	GTR	CSI, PF	PF	GTR	IV Topotecan	CSI, boost	Temozolor
18	Standard	M0	Desmoplastic	GTR	CSI, PF	ST, Ventricle	None	IV Topotecan,Temozolomide,VP16	Focal	IV Topotec Temozolor
19	Standard	M0	Classic	GTR	CSI, PF	Ventricle	None	Carboplatin ,VP16/ Temozolomide	Focal	Temozolor
20	Standard	M0	Classic	GTR	CSI, PF	Ventricle	Biopsy	Carboplatin, VP16/ Cyclophosphamide, VP16	Focal	Temozolor
21	High	M3	Anaplastic	GTR	CSI, PF	ST	STR	None	Focal	Temozolor
22	High	M3	Classic	STR	CSI, PF	ST	None	Temozolomide,VP16	CSI, boost	Temozolor
23	High	M1	Anaplastic	GTR	CSI, PF	ST	STR	None	Focal	None
24	**Infant**	**M0**	**Desmoplastic**	**GTR**	**PF**	**Isolated SC**	**None**	**None**	**CSI, boost**	**5D-IV Topo**

Abbreviations: Anti VEGF: Anti–vascular endothelial growth factor therapy, Ccnu: Lomustine, CSI: craniospinal irradiation, HFSRT: hypofractionated stereotac gross-total resection, IV: intraventricular, LS: Leptomeningeal Spread, MTX: Methotrexate, PF: Posterior Fossa, RT1: first course of radiotherapy at diagnosis, F radiotherapy, RT3: Third course of radiotherapy, SC: Spinal Cord, ST: Supratentorial, STR: subtotal resection, VP16: etoposide, 5D: Fenofibric acid-Celecoxib-T Cyclophosphamide-Etoposide-Bevacizumab. *: CSI, boost, **: Focal. It highlighted the patients who are alive at the moment of the present study.

Table 2
Re- irradiation timing per risk group.

	SR	HR	Infants
Median age at RT2	11.25 years (range 7.1–12.7)	12.1 years (range 4.9–17.4)	5.3 years (range 4.7–7.6)
Time from first failure to RT2	16.3 months (range 1.3–28.9)	6.7 months (range 0.2–21.6)	3.6 months (range 0.8–18.6)
Median time from RT1 to RT2	3.29 years (range 0.7–4.8)	3.29 years (range 0.8-5)	2.85 years (range 1.3–3.9)
Abbreviations: HR: high risk.; SR: standard risk.			

Table 3
Cumulative radiotherapy dose and overall survival correlation

ID	Interval between RT1-RT2 (years)	Cumulative Dose Spine (Gy)	Cumulative Dose Supratentorial (Gy)	Cumulative Dose Posterior Fossa (Gy)	OS (from date of diagnosis in years)	OS (from date of relapse in years)	OS (from RT2 in years)	Vital status
1	3,3	**45**	61,2	75,6	4,4	2,9	1,01	DOD
2	3,3	**45**	61,2	75,6	5,4	3,6	1,97	DOD
3	3,1	**45**	68,4	82,8	4,4	2,5	1,12	DOD
4	3,2	23,4	48,4	79	3,9	2,2	0,64	DOD
5	2,7	36	36	90	5,8	4,1	2,52	DOD
6	2,5	**43.2**	59.2	73.8	3,6	1,6	1,05	DOD
7	4,8	23.4	34,2	54	5,7	1,8	0,65	DOD
8	5	**57,6**	57,6	77,4	10,9	7,5	5,78	NED
9	0,8	**52,2**	39,6	75,6	1,6	0,8	0,70	DOD
10	0,8	**57,6**	66,6	57,6	7,5	6,5	6,52	NED
11	1,9	66	36	55,8	4	2	1,84	DOD
12	1,3	45	36	64,8	6,5	4,8	4,74	NED
13	3,4	**57,6**	66,6	67	5	3	1,24	DOD
14	3.0	21,6	37.8	55,8	7,9	4,6	4.39	DOD
15	2,7	**59,4***	57,6	97,2	8,3	5	4,98**	NED
16	4,2	**57,6**	77,4	57,6	6	4	1,63	Alive with disease
17	3,3	**45**	45	95,4	4,2	1,1	0,69	DOD
18	1,9	53.4	63	54	4	2,1	1,99**	DOD
19	2,3	26	56	60	2,9	1	0,45	DOD
20	3,3	N/A	N/A	N/A	3,8	0,9	0,39	DOD
21	1.3	23,4	63	54	1,7	0.3	0.26	DOD
22	3,6	**57,6**	66,6	77,4	5,4	3	1,73	DOD
23	1	36	75,6	55,8	1,2	0,2	0,12	Dead***
24	3.9	46.8	36	70	5,6	1,2	1,14	NED

Abbreviations: DOD: Dead of disease, NED: No evidence of disease, OS: Overall Survival, RT1: first course of radiotherapy at diagnosis, RT2: second course of radiotherapy, *: Dose achieved including the 3rd course of radiation, **: Patients who received a 3rd course of radiation, ***: Died due to systemic virus infection. It highlighted the patients who received 2 courses of CSI.

Figures

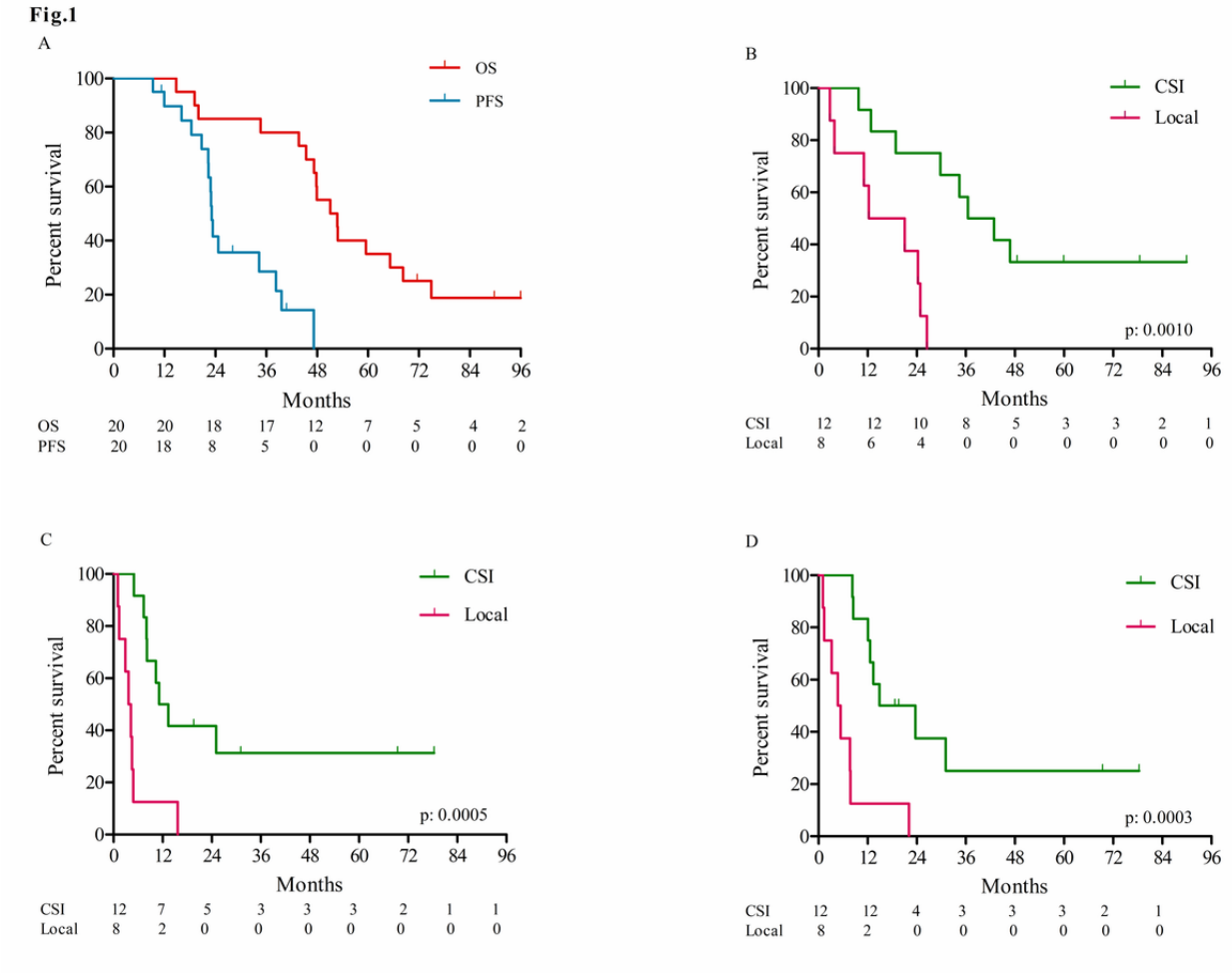

Figure 1

Outcomes for re-irradiated relapsed medulloblastoma treated with CSI upfront. Kaplan–Meier survival curve of (A) PFS and OS from initial medulloblastoma diagnosis for re-irradiated relapsed medulloblastoma. Kaplan–Meier estimates of (B) OS from first recurrence for re-irradiated relapsed medulloblastoma treated with focal re-irradiation vs. re-CSI. Kaplan–Meier estimates of (C) PFS and (D) OS from RT2 for re-irradiated relapsed medulloblastoma treated with focal re-irradiation vs. re-CSI. P-values are determined using the log-rank method.

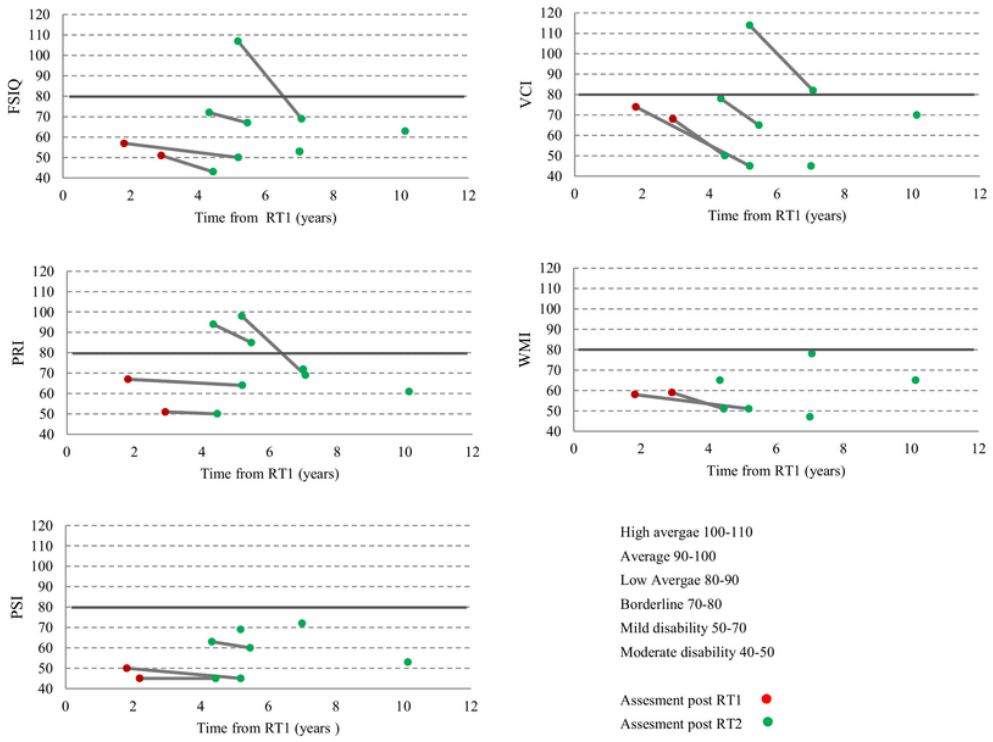

Figure 2

Declines in neurocognitive status over time in 6 relapsed medulloblastoma survivors who received 2 or more courses of radiotherapy. Estimated declines in (A) the Full-Scale Intelligence Quotient (FSIQ) over time (years) since RT1. (B) Processing Speed Index (PSI), (C) Perceptual Reasoning/Organization Index (PRI), (D) Working Memory index (WMI), and (E) Verbal Comprehension Index (VCI) in linear term model. Lines represent patients who were seen for longitudinal intellectual assessments; each red dot represents a patient who was seen once after RT1; each green dot represents a patient who was seen once after RT2. The dark gray line at 80 represents the delineation between borderline and low average.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TABLE1supplementarydata.docx
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