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Salvage Re-Irradiation after Complex Treatment in Childhood Leptomeningeal Metastatic Medulloblastoma-Clinical Case with Literature Review

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ABSTRACT

Leptomeningeal metastases diagnosed in a child with high-risk medulloblastoma immediately after surgery are very rare. The primary treatment is extremely complicated, namely the assessment of the duration of systemic and intraventricular chemo- and immunotherapy, as well as the timing of starting craniospinal radiotherapy. Even more complicated is the question "When in time, in what volume and with what cumulative doses should salvage re-radiotherapy be performed in a child with long-term observed leptomeningeal spread diagnosed immediately after the initial surgery?". Based on a clinical case of a child with high-risk medulloblastoma and a literature review, we aim to answer the above questions.

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Introduction

Leptomeningeal disease (LMD), also known as neoplastic meningitis, leptomeningeal carcinomatosis, or carcinomatous meningitis, is a rare cancer complication in which malignant cells infiltrate the layers of the central nervous system (CNS), known as meninges, and lead to significant morbidity and mortality [1]. In medulloblastoma (MB), the commonest childhood malignant brain tumour, 30% present with LMD and 60% have LMD at relapse [2]. Leptomeningeal dissemination (LMD) is the defining pattern of metastasis for MB. Although LMD is responsible for virtually 100% of MB deaths, it remains the least well-understood part of MB pathogenesis [3]. Historically, craniospinal radiotherapy (CSRT) has been the standard approach to treating the risk of, and actual LMD, complicating brain tumours. Indeed, it offered the first examples of "cure" in MB [4,5]. Despite this treatment some patients will experience relapse and re-irradiation is an important part of the salvage therapy [6]. Intra-CSF drug delivery in brain tumours is complicated by post-operative changes and the co-existence of ventricular peritoneal shunts [7]. A cohort of patients with leptomeningeal spinal metastases (LSM) treated with radiotherapy (RT) with definitive intent, and the only available data from the proton setting, is described [8]. In this article, we pose the main question - When in time and with what cumulative doses should salvage repeat radiotherapy be performed in a child with leptomeningeal spread diagnosed immediately after the initial surgery?

Clinical Case

This is a 7-year-old child diagnosed with medulloblastoma in early 2022 with complaints of morning vomiting, nausea, headache and drowsiness, instability during movement. MRI of the head and spine (03.02.2022) revealed obstructive hydrocephalus with the presence of a tumor in the cerebellum. in the cerebrospinal fluid from a staging lumbar puncture (09.03.2022) 6 tumor cells/ml2 are recorded. According to Chang's modified classification, this CSF finding corresponds to M1 dissemination. After craniotomy, a visibly total tumor extirpation was performed. The pathohistological diagnosis was a classic variant of medulloblastoma, molecular group 3 (Medulloblastoma, SHH-activated and TP53-mutant), second methylation subclass with high risk. On 14.03.2022, the staging MRI detected multiple leptomeningeal metastases supra, infratentorially and along the course of the spinal cord - M3 stage. Treatment was followed by 6 courses of Chemotherapy (ChT) according to the HIT Med Guidance 2017 protocol, including intraventricular Methotrexate. In September and October 2022, the child was sent to the Proton Therapy Center in Trento, Italy, where proton craniospinal radiotherapy (CSRT) was performed to 36 Gy with a boost in the primary tumor to 54 Gy and a boost in the lumbar spinal metastasis to 45 Gy (Figure 1).10 months after RT craniospinal MRI / 24-08-23 found recurrent leptomeningeal spread - tumor formation in the area of the caudate nucleus measuring 17/13 mm compared to 10/8 mm on the transitional examination. Identical newly appeared lesions in the right lateral ventricle, right temporal and right frontal parasagittal. It was considered to start HT with Irinotecan, Temozolomide and Avastin/ Bevacizumab. On 30.11. 23 an MRI was performed with data on the disease staging. Therapy with Irinotecan, Temozolomide and

Avastin/Bevacizumab continues. On 29.02.24, the control MRI showed an increase in two of the traceable subependymal nodules in the area of the caudate nucleus and the right lateral ventricle, which necessitated the initiation of intraventricular administration of Cytarabine / Depocyte/ via Ommaya reservoir. On 15.03.24, a course of Irinotecan and Bevacizumab was conducted. From 28.05. 24 he was on the MEMMAT regimen, and on 27.08.24 the control craniospinal MRI revealed progression of the disease (Figure 2) and after two months, a new MRI revealed rapid progression in the size of the MRI visible nodular lesions in the caudate nucleus and bilateral retrobulbar areas (Figure 3). After 2 years of previous radiation treatment, the child was referred for re-irradiation. Given the craniospinal radiotherapy performed with a boost in the macroscopically visible spinal metastases to a dose of 40 Gy, we considered it risky to re-irradiate the spinal axis. We performed the intensity modulated re-irradiation in the whole brain area with a daily dose (DD) 1.5 Gy to a total dose (TD) 22.5 Gy with a simultaneous boost in the areas of the MRI-visible leptomeningeal nodular lesions / caudate nucleus, anterior frontal and bilateral temporal retrobulbar/ with a DD 2.26 Gy to a TD of 34 Gy/ EQD2 36,21Gy (Figure 4 and Figure 5). During the entire RT, verification of the radiation fields was performed with CB/CT. In Figure 6, we compare the CB/CT verification image from the first day of irradiation with that from the last day, which shows a visible reduction of the nodular lesion in the area of the left caudate nucleus. Re-irradiation (re-RT) was performed simultaneously with Temodal tablets according to the scheme. The child tolerated the radiation well, without acute neurological symptoms. After 1 month of completing re-RT, a control MRI was performed, which did not show hydrocephalus, with significant regression of the nodular lesion in the head of the caudate nucleus, now 11 mm, and before radiotherapy 2.56 cm (clearly visible in Figure 4 and Figure 5). After 1.5 months of completing re-RT, the child was exhausted, without strength, drowsy, with uncoordinated gait, slightly staggering and with tremor of the right limbs. After a few days he had a seizure and was hospitalized in the Neurosurgery Department. Tumor cells were found again in the cerebrospinal fluid and the child died in a comatose state after 1 week.

Discussion

In 2021, a new WHO classification of central nervous system tumors was carried out, where medulloblastoma was classified into four molecular groups/ 1/ Medulloblastoma, WNT-activated; 2/Medulloblastoma, SHH-activated and TP53-wildtype; 3/ Medulloblastoma, SHH-activated and TP53-mutant; 4/ Medulloblastoma, non-WNT/non-SHH [9]. These four subgroups have distinct transcriptional profiles, copy-number aberrations, somatic mutations, and clinical outcomes [10]. The presented clinical case has a pathohistological diagnosis of a classic variant of medulloblastoma from molecular group 3 (medulloblastoma, SHH-activated and TP53-mutant) and a second methylation subclass, which corresponds to high-risk MB. Recent experimental evidence challenges the belief that dissemination into the cerebrospinal fluid (CSF) is the sole mechanism of LMD, and reveals an alternative scheme in which medulloblastoma cells can enter the bloodstream and subsequently end up in the leptomeninges [11].

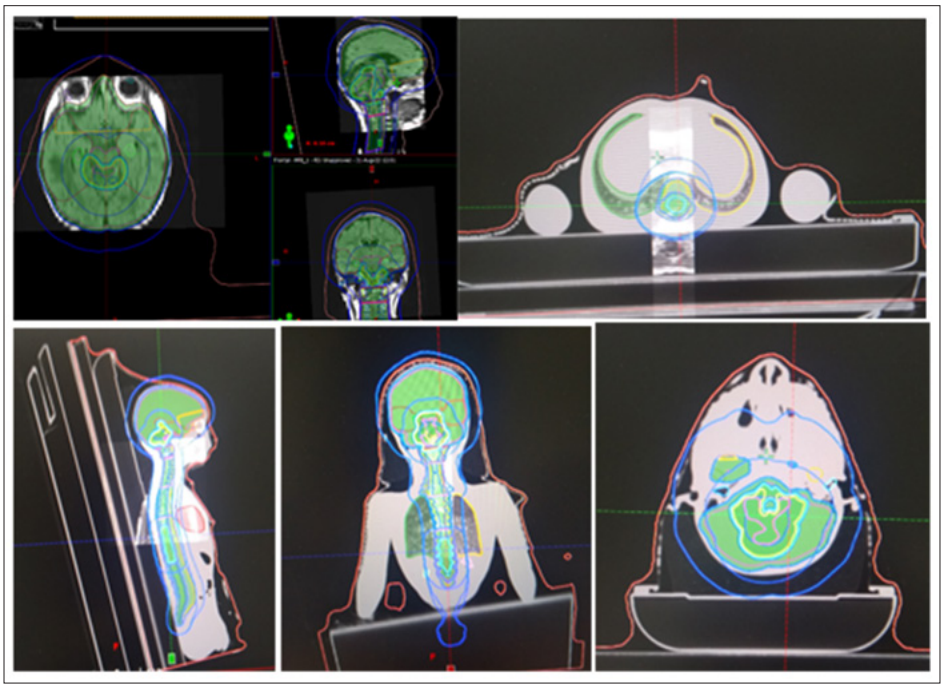

Figure 1: Proton Craniospinal Radiotherapy (CSRT) up to 36 Gy with Dose Escalation in the Primary Tumor up to 54 Gy and dose Escalation in Lumbar Spinal Metastases up to 45 Gy

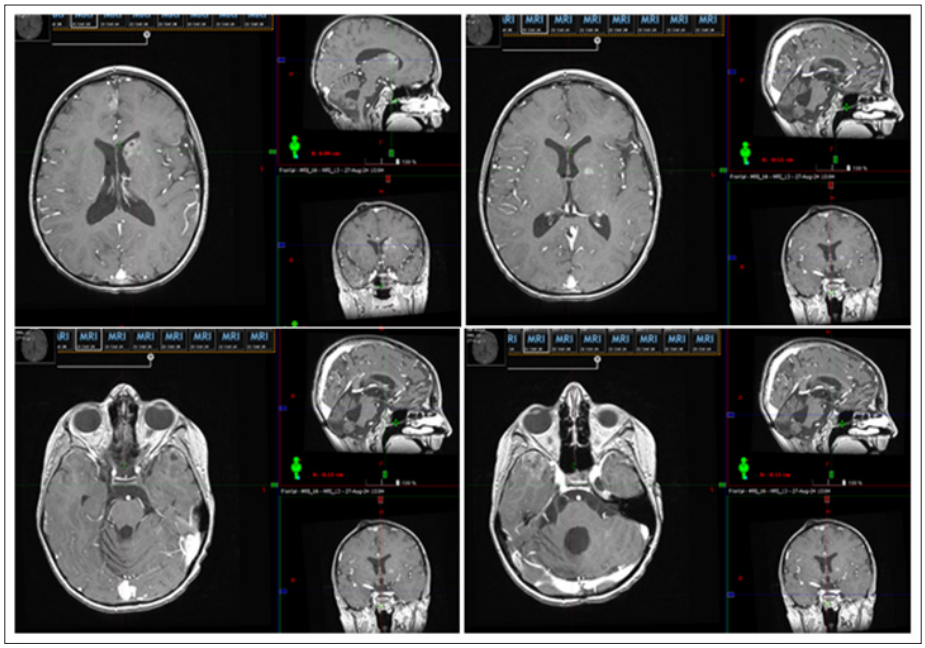

Figure 2: The Control Brain MRI on 27.08.24 Revealed Progression of the Leptomeningeal Disease

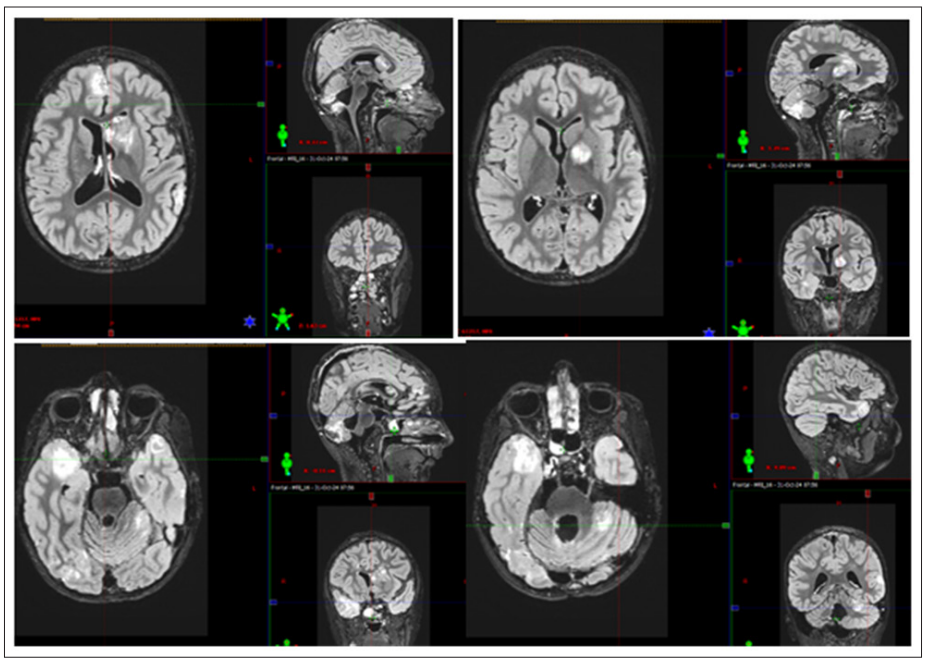

Figure 3: Magnetic Resonance Imaging (MRI) from November 2024 with Rapid Progression in Size of MRI Visible Nodular Lesions in the Caudate Nucleus and Bilaterally in the Retrobulbar Brain Regions.

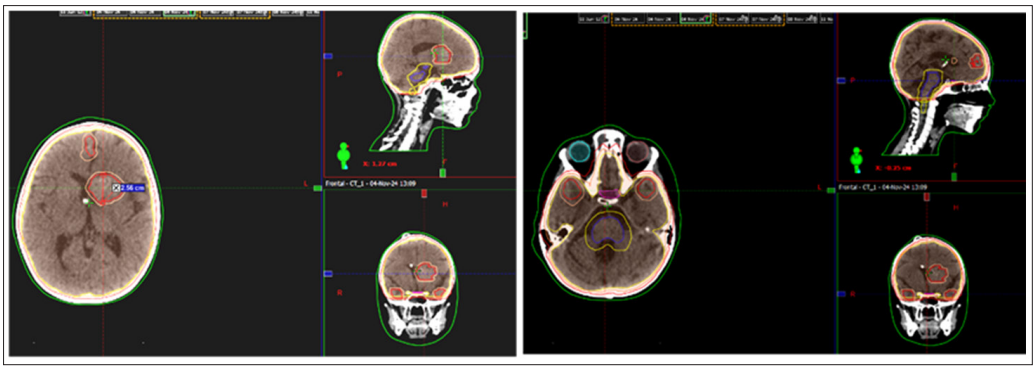

Figure 4: Contouring of the Whole-Brain Re-Irradiation with Delineation of Visible Nodular Lesions in the Caudate Nucleus and in the Retrobulbar Brain Bilaterally Regions, where a Simultaneous Boost will be Performed

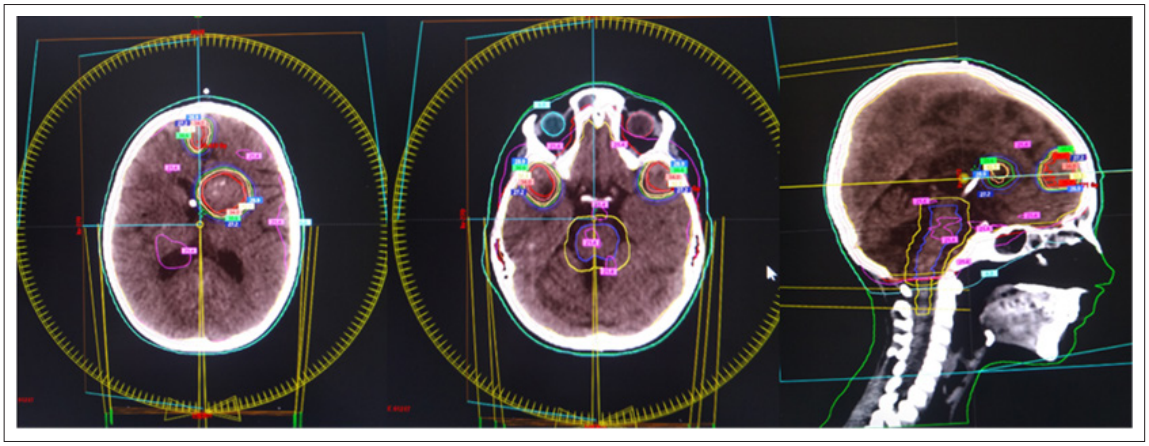

Figure 5: The Intensity Modulated Re-Irradiation in the whole Brain area with a Daily Dose (DD) 1.5 Gy to a total dose (TD) 22.5 Gy with a Simultaneous Boost in the Areas of the MRI-Visible Leptomeningeal Nodular Lesions / Caudate Nucleus, Anterior Frontal and Bilateral Temporal Retrobulbar/ with a DD 2.26 Gy to a TD of 34 Gy/ EQD2 36,21Gy.

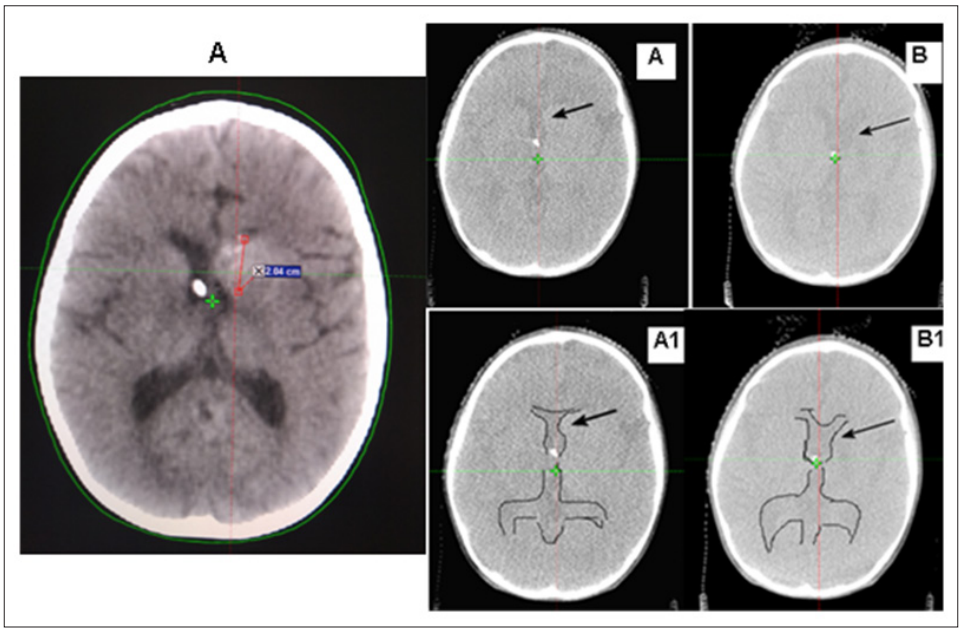

Figure 6: A/B: Comparison between the CB/CT Verification Images on the first day of Irradiation with the one on the Last Day, which Shows a Visible Reduction of the Nodular Lesion in the Area of the Left Caudate Nucleus. A1/B1- For better Visibility, the Lateral Ventricles are Outlined, and the Black Arrow Points to the Reduction of the Caudate Nucleus.

Leptomeningeal Disease (LMD) is commonly characterized as the metastatic involvement of various meningeal regions—the arachnoid mater, subarachnoid space, and pia mater—defined as the leptomeningeal layer [12]. In the child diagnosed with high-risk medulloblastoma with subarachnoid spinal metastases, all possible treatments have been exhausted - surgery, systemic ChT, craniospinal radiotherapy (CSRT) with accelerated protons and a boost in the primary tumor and macroscopically visible spinal metastases, immunotherapy, intraventricular therapy with Cytarabine, as well as antiangiogenic therapy. The antiangiogenic therapy is a new therapeutic option for solid malignancies and evaluates the effect of using biweekly intravenous bevacizumab in combination with five oral drugs (thalidomide, celecoxib, fenofibrate, and alternating cycles of daily low-dose etoposide and oral cyclophosphamide), supplemented with alternating courses of intrathecal etoposide and cytarabine. Several mechanisms for the general onset of LMD have been purported: (1) direct invasion via surrounding structures, such as the dura mater, bone, or nerves; (2) hematogenous spread often by way of venous vasculature; and, lastly, (3) entry of the fenestrated pores of the choroid plexus typically permitting solute transport [13,14].

Primary Complex Treatment in older children is stratified into high- and average-risk groups, depending on clinical prognostic markers. The most significant prognostic factor following age is the presence of metastatic disease, classifying these patients as high-risk. The extent of surgical resection is important and the consensus is that surgery should be as extensive as safely achievable [15]. In the cases of medulloblastoma, the cerebrospinal fluid pathway is the most important route of metastasis. The extent of metastasis is subdivided to Mo, Ml, M2, M3 /112. The Chang staging system was used: M0 indicates no evidence of gross residual tumor or metastasis, M1 is the presence of microscopic tumor cells in the cerebrospinal fluid, M2 is gross nodular seeding within the central nervous system other than the spinal space, M3 is gross nodular seeding in the spinal subarachnoid space, and M4 is metastasis outside the cerebrospinal axis [16]. The ASCO post "No Event-Free Survival Difference With Chemotherapy Before vs

After Radiotherapy in Children With High-Risk Medulloblastoma" from by Matthew Stenger /2013 discusses a study (POG 9031) that evaluated the treatment effect of chemotherapy before vs after radiotherapy after surgery in children with high-risk medulloblastoma. The investigators found no difference in 5-year event-free survival between the two strategies. Chemotherapy before radiation does not confer a survival advantage compared with radiotherapy before chemotherapy [17]. The HIT-SIOP PNET-4 study comparing the treatment effect in children with standard-risk medulloblastoma treated by postoperative hyperfractionated or conventionally fractionated radiotherapy, the prognosis was worse in patients in whom radiotherapy was delayed by more than 7 weeks. Excellent survival rates were reported in patients with no postoperative residual tumor and no delay in RT [18]. Results in children with intermediate- and high-risk medulloblastoma who started the modified SIOP/UKCCSG PNET-3 chemotherapy protocol, in which radiotherapy was started as soon as possible after surgery, are reported. The 5-year event-free survival of patients for delayed (beyond 7 wk) and non-delayed radiotherapy was 59.7±14.6% and 76.7±7.4% (P=0.385), respectively, without considering the risk group [19]. In the presented clinical case, the initial craniospinal radiotherapy was significantly delayed after the surgery, as it was performed after 6 chemotherapy courses per HIT Med Guidance 2017 protocol. The above-cited authors recommend craniospinal radiotherapy in high-risk medulloblastoma after 37 days from the surgery. Clinical studies treating pediatric and adult solid tumors, such as glioblastoma (GBM), with a triple-drug regimen of temozolomide (TMZ), bevacizumab (BEV), and irinotecan (IRI) [TBI] have demonstrated various efficacies, but with no unexpected toxicities [20].

The Re-Irradiation of Recurrent Medulloblastoma can prove challenging due to a concern of exceeding radiation tolerances and late treatment toxicities. Normal brain tissue can tolerate a total dose of 100 Gy; therefore, re-irradiation of patients risks exceeding this limit and subsequently leading to necrosis of the brain tissue [21]. The modification of radiation fields using Intensity-Modulated Radiation therapy (IMRT), tomo-therapy and proton therapy offer reductions in scatter dose radiation and greater precision of tumour bed volumes but cannot compensate for the radiation brain injury within boosted fields, consequent upon cranio-spinal radiotherapy [22,23].

Treatment for LMD offers conventional cancer treatment in the forms of surgery, radiotherapy, and chemotherapy. Surgical intervention primarily involves the installation of interventricular delivery devices (i.e., the Ommaya reservoir) or management of LMD complications, such as hydrocephalus and addressing excessive intracranial pressure (ICP); this entails a ventriculoperitoneal shunt (VPS)-dependent manner of draining excess CSF [24]. One approach, due to the poor penetration of drugs into the cerebrospinal fluid, is to use extremely systemic dosing, such as high-dose methotrexate with folic acid salvage therapy in leukemias [25] or high-dose multicomponent chemotherapy with stem cell salvage therapy in brain tumors [26], to attempt to achieve higher concentrations of cytotoxic drugs in the CNS. The combination of BEV with more conventional therapy schemes with chemo- and/or radiotherapy may be a palliative treatment option for patients with leptomeningeal dissemination of brain tumors [24]. Increased proliferation through autocrine VEGF signalling under cell culture conditions has been described both for glioblastoma and medulloblastoma cells [27,28]. Encouraging therapeutic responses have been documented in children with high-risk medulloblastomas progressing early after initial surgery, following radiotherapy with a DOD of 1.7 Gy, 5 days/week, to a total dose of 55/56 Gy, together with temozolomide 90 mg/m2/day for 42 days [29]. While radiation therapy is an essential component of multimodality therapy in the treatment of newly diagnosed MB, there has been much debate about the use of irradiation at the time of progression because of the potential for toxicity and uncertainty about its ability to improve overall survival [30-32].

Re-Irradiation is an option for other types of brain tumors, there is a lack of data in the literature about the re-irradiation of recurrent medulloblastoma in children [33]. Several studies report that re-irradiation of large volumes due to leptomeningeal spread or repeated re-irradiation due to new recurrencies is futile [30,34]. Further research, including third-phase randomized controlled trials, must investigate the appropriate type and dose of re-irradiation therapies for molecularly-stratified patients with recurrent medulloblastoma. The development and universal adoption of guidelines are essential for managing recurrent medulloblastoma with careful monitoring of toxicities [35]. Bakst et al. reported re-irradiation with a median dose of 30Gy (19.8-45Gy) and high-dose chemotherapy after re-resection of recurrent medulloblastoma with overall disease-free survival of 46% at five years after initial recurrence . The median cumulative total dose of radiotherapy to the brain or spine was 84Gy (65-98.4Gy), and intensity-modulated radiation therapy (IMRT) was used in 54% [30]. Intracranial recurrencies should be boosted aiming at a total re-irradiation dose of 40-45 Gy, i.e. a boost of 1,8 Gy x 7-10 fractions. But the dose of the boost has to be individualised after considering organs at risk nearby and cumulative doses in the area [36]. Craniospinal re-radiation is appropriate for recurrent childhood medulloblastoma, especially those with local brain recurrences [37]. In selected cases, re-radiation for recurrent MB achieves 5-year progression-free survival and overall survival from first recurrence of 48% and 65%, respectively [38]. The median time interval between radiotherapy courses is 2.0 years (range 0.3–16.5). For the initial RT, the mean total radiation dose equivalent to a single 2Gy fraction (EQD2) was 63.7 Gy (range 27.6–74.8), and for re-RT, the mean EQD2 was 53.1 Gy (range 18.6–70.1) [39]. The median time interval from primary to recurrent RT was 49.5 months (range 24–98 months) with a median total biologically effective dose (BED) of 117 Gy (range 78–132 Gy) [40]. Five patients from 10 to 27 years old relapsed focally and progressed under chemotherapy with a time recurrence ranged from 2 to 15 years after initial diagnosis. Patients were then treated with 3-dimensional conformal reirradiation focused on the relapsed disease with a median dose of 28 Gy (1.8 Gy per fraction) and concomitant temozolomide (75 mg/m2/d) alone or as part of a multidrug metronomic regimen.The median follow-up was 28 months.No neurological toxicity was observed [41].

The Radiation is Typically Indicated for LMD with the sole aim of palliation This is implemented in the form of whole brain radiation therapy (WBRT) for cranial afflictions, with spinal localization utilizing traditional fractionated radiation [42]. In disseminated neuraxis disease salvage CSI dose was 36 Gy in 20 fractions in all 6 patients. IMRT was used to treat the cranial contents excluding the previously treated area [43]. The median dose for the second re-irradiation in recurrent medulobllastoma was 36 Gy (range 18-54 Gy). The median total maximum cumulative dose was 91.9 Gy (range: 73.8 Gy to 109.8 Gy). There were no differences in the incidence of hemorrhage, pituitary or thyroid dysfunction between patients who did or did not receive second course of RT, however the data suggested an association between RT and higher rate of necrosis (p=0.047) [44]. In the presented metastatic medulloblastoma, after the combined treatment with the use of all possible therapeutic options, a survival

of 2 years and 6 months was observed. Throughout the entire time, reductions and progressions of the leptomeningeal brain metastases were reported against the background of systemic and intraventricular chemo- and immunotherapy, and in the case of the last progression, the child was referred for re-irradiation. From the re-irradiation, the biologically effective dose (BED) in the MRI visible leptomeningeal lesion in the caudate nucleus area at an alpha/beta ratio of 2 Gy for normal brain structures was 72.42 Gy, and the total BED with the first irradiation was 108.42 Gy. The total BED from the two irradiations in the medulloblastoma tumor cells at an alpha/beta ratio of 10 Gy was 70.7 Gy. Re-irradiation was performed simultaneously with Temodal tablets according to the scheme.

In LMD, Symptomatic Subacute Leukoencephalopathy (confusion, somnolence or irritability, ataxia, dementia and tremor or myelopathy are rare events, and are more common with concurrent systemic treatment and/or radiotherapy [45-48]. Delayed complications occurred in 58%, with leukoencephalopathy equally affecting patients exposed and patients not exposed to cranial irradiation. The median survival of the whole group was 23 months [49]. The caudate nucleus is an important structure in the human brain whose function is related not only in planning the execution of movement, but also in learning, memory, reward, motivation, emotion, and romantic interaction [50,51]. The clinical features of Creutzfeldt-Jakob disease (CJD) are expressed by rapid progressive cognitive decline and myoclonic jerks, and MRI brain showing cortical ribboning and high signal in the caudate nucleus. Seizures, ranging from simple seizures to status epilepticus, have also been reported in patients with Creutzfeldt-Jakob disease [52].

We believe that as a result of the cumulative effect of re-irradiation of the CNS, combined with Temodal and the previous prolonged intraventricular chemo- and immunotherapy, leukoencephalopathy with pronounced neurotoxicity in the caudate nucleus area occurred. The Figure 6 shows that the medulloblastoma leptomeningeal cells in the caudate nucleus were locally destroyed, but its neuronal structures suffered radiation toxicity, which we observed 1.5 months after the end of re-irradiation.

Conclusion

As a result of the presented clinical case and the review of the literature, we can draw the following conclusions: 1/ In high-risk medulloblastoma, due to the fact that medulloblastoma cells are extremely radiosensitive, the initial craniospinal radiotherapy should be performed no later than 37 days after surgery. 2/ Re-irradiation in medulloblastoma leptomeningeal metastases should be performed at least one year after the primary craniospinal radiotherapy, due to the fact that prolonged systemic chemotherapy, intraventricular and intrathecal chemo- and immunotherapy before re-irradiation significantly increase the neurotoxicity of normal brain structures. 3/ In leptomeningeal disease, despite or without multiple courses of systemic chemotherapy, as well as intraventricular immuno- or chemotherapy, the total BED in the CNS should not exceed 117 Gy in order to minimize acute and subacute radiation neurotoxicity.

References

1. Buszek SM, Chung C (2019) Radiotherapy in Leptomeningeal Disease: A Systematic Review of Randomized and Non-Randomized Trials. Front. Oncol 9: 1224.
2. Suki D, Hatiboglu MA, Patel AJ, Weinberg JS, Groves MD, et al. (2009) Comparative risk of leptomeningeal dissemination of cancer after surgery or stereotactic radiosurgery for a single supratentorial solid tumor metastasis. Neurosurgery 64: 664-746.
3. Fults DW, Taylor MD, Garzia L (2019) Leptomeningeal dissemination: a sinister pattern of medulloblastoma growth. J Neurosurg Pediatr 23: 613-621.
4. Paterson E, Farr RF (1953) Cerebellar medulloblastoma: Treatment by irradiation of the whole central nervous system. Acta radiol 39: 323-336.
5. Bloom HJ, Wallace EN, Henk JM (1969) The treatment and prognosis of medulloblastoma in children. A study of 82 verified cases. Am J Roentgenol Radium Ther Nucl Med 105: 43-62.
6. Wetmore C, Herington D, Lin T, Onar-Thomas A, Gajjar A, et al. (2014) Reirradiation of recurrent medulloblastoma: does clinical benefit outweigh risk for toxicity? Cancer 120: 3731-3737.
7. Walker DA, Meijer L, Coyle B, Halsey C (2020) Leptomeningeal malignancy of childhood: sharing learning between childhood leukaemia and brain tumour trials. Lancet Child and Adolescent Health 4: 242-250.
8. Ray GL, Buchsbaum JC, McMullen KP, Simoneaux RV, Hines M, et al. (2013) Definitive treatment of leptomeningeal spinal metastases in children. Pediatr Blood Cancer 60: 1839-1841.
9. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, et al. (2021) The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol 23: 1231-1251.
10. Morrissy AS, Garzia L, Shih DJ, Zuyderduyn S, Huang X, et al. (2016) Divergent clonal selection dominates medulloblastoma at recurrence. Nature 529: 351-357.
11. Fults DW, Taylor MD, Garzia L (2019) Leptomeningeal dissemination: a sinister pattern of medulloblastoma growth. J Neurosurg Pediatr 23: 613-621.
12. Nguyen A, Nguyen A, Dada OT, Desai PD, Ricci JC, et al. (2023) Leptomeningeal Metastasis: A Review of the Pathophysiology, Diagnostic Methodology, and Therapeutic Landscape. Curr Oncol 30: 5906-5931.
13. Nayar G, Ejikeme T, Chongsathidkiet P, Elsamadicy AA, Blackwell KL, et al. (2017) Leptomeningeal disease: Current diagnostic and therapeutic strategies. Oncotarget 8: 73312-73328.
14. Batool A, Kasi A (2023) Leptomeningeal Carcinomatosis. StatPearls Publishing https://pubmed.ncbi.nlm.nih.gov/29763037/.
15. Albright AL, Wisoff JH, Zeltzer PM, Boyett JM, Rorke LB, et al. (1996) Effects of medulloblastoma resections on outcome in children: a report from the Children's Cancer Group. Neurosurgery 38: 265-271.
16. Dufour C, Beaugrand A, Pizer B, Micheli J, Aubelle MS, et al. (2012) Metastatic Medulloblastoma in Childhood: Chang's Classification Revisited. Int J Surg Oncol 2012: 245385.
17. Tarbell NJ, Friedman H, Polkinghorn WR, Yock T, Zhou T, et al. (2013) High-risk medulloblastoma: a pediatric oncology group randomized trial of chemotherapy before or after radiation therapy (POG 9031). J Clin Oncol 31: 2936-2941.
18. Lannering B, Rutkowski S, Doz F, Pizer B, Gustafsson G, et al. (2012) Hyperfractionated versus conventional radiotherapy followed by chemotherapy in standardrisk medulloblastoma: Results from the randomized multicenter HIT-SIOP PNET 4 trial. J Clin Oncol 30: 3187-3193.
19. İbrahim Kartal, Ayhan Dağdemir, Oğuz Salih Dinçer, Hülya Kangal Şimşek, Alper Uygun, et al. (2023) Treatment Outcomes of Childhood Medulloblastoma with the SIOP/UKCCSG PNET-3 Protocol. Indian J Pediatr 90: 1116-1122.
20. Mayer R, Sminia P (2008) Reirradiation tolerance of the human brain. Int J Radiat Oncol Biol Phys 70: 1350-1360.

21. Metts J, Harrington B, Salman E, Bradfield SM, Flanary J, et al. (2022) A phase I study of irinotecan and temozolomide with bevacizumab in children with recurrent/refractory central nervous system tumors. Childs Nerv Syst 38: 919-928.
22. Merchant TE, Pollack IF, Loeffler JS (2010) Brain tumors across the age spectrum: biology, therapy, and late effects. Semin Radiat Oncol 20: 58-66.
23. Ramaswamy V, Remke M, Bouffet E, Bailey S, Clifford SC, et al. (2016) Risk stratification of childhood medulloblastoma in the molecular era: the current consensus Vol. 131, Acta Neuropathologica 131: 821-831.
24. Burger MC, Zeiner PS, Jahnke K, Wagner M, Mittelbronn M, et al. (2016) Addition of Anti-Angiogenetic Therapy with Bevacizumab to Chemo- and Radiotherapy for Leptomeningeal Metastases in Primary Brain Tumors. PLoS One 11: e0155315.
25. Murphy SB, Bowman WP, Abromowitch M, Mirro J, Ochs J, et al. (1986) Results of treatment of advanced-stage Burkitt's lymphoma and B cell (SIg+) acute lymphoblastic leukemia with high-dose fractionated cyclophosphamide and coordinated high-dose methotrexate and cytarabine. J Clin Oncol 4: 1732-1739.
26. Main C, Wilson JS, Stevens SP, Houlton AE, English M, et al. (2015) The role of high-dose myeloablative chemotherapy with haematopoietic stem cell transplantation (HSCT) in children with central nervous system (CNS) tumours: protocol for a systematic review and meta-analysis, Systematic Reviews 4: 168.
27. Knizetova P, Ehrmann J, Hlobilkova A, Vancova I, Kalita O, et al. (2008) Autocrine regulation of glioblastoma cell cycle progression, viability and radioresistance through the VEGF-VEGFR2 (KDR) interplay. Cell cycle 7: 2553-2561.
28. Slongo ML, Molena B, Brunati AM, Frasson M, Gardiman M, et al. (2007) Functional VEGF and VEGF receptors are expressed in human medulloblastomas. Neuro-oncology 9: 384-392.
29. Sterba J, Pavelka Z, Slampa P (2002) Concomitant radiotherapy and metronomic temozolomide in pediatric high-risk brain tumors. Neoplasma 49: 117-120.
30. Bakst RL, Dunkel IJ, Gilheeney S, Khakoo Y, Becher O, et al. (2011) Reirradiation for recurrent medulloblastoma. Cancer 117: 4977-4982.
31. Chojnacka M, Skowronska-Gardas A (2004) Medulloblastoma in childhood: Impact of radiation technique upon the outcome of treatment. Pediatr Blood Cancer 42: 155-160.
32. Veninga T, Langendijk HA, Slotman BJ, Rutten EH, van der Kogelet AJ, et al. (2001) Reirradiation of primary brain tumours: survival, clinical response and prognostic factors. Radiother Oncol 59: 127-137.
33. Chojnacka M, Skowroriska-Gardas A, Pedziwiatr K, Marzena Morawska-Kaczyńska, Marta Perek, et al. (2011) Re-irradiation of relapsed brain tumors in children. Rep Pract Oncol Radiother 17: 32-37.
34. Tsang DS, Sarhn N, Ramaswamy V, Nobre L, Yee R, et al. (2019) Re-irradiation for children with recurrent medulloblastoma in Toronto, Canada: a 20-year experience. J Neurooncol 145: 107-114.
35. Giakoumettis G, Mantzavinou A, Moschos G, Dimitrios Giakoumettis, Antonio Capizzello (2022) Re-irradiation of Pediatric Medulloblastoma: A Case Report and Systematic Review. Cureus 14: e31585.
36. Embring A, Blomstrand M, Asklid A, Nilsson MP, Agrup M, et al. (2023) Re-irradiation in Paediatric Tumours of the Central Nervous System: National Guidelines from the Swedish Workgroup of Paediatric Radiotherapy. Clin Oncol R Coll Radiol 35: 571-575.
37. Derek S Tsang, Nasim Sarhan, Vijay Ramaswamy, Liana Nobre, Ryan Yee, et al. (2019) Re-irradiation for children with recurrent medulloblastoma in Toronto, Canada: a 20-year experience. Journal of Neuro-Oncology 145: 107-114 .
38. Bakst RL, Dunkel IJ, Gilheeney S, Yasmin Khakoo, Oren Becher, et al. (2011) Reirradiation for recurrent medulloblastoma. Cancer 117: 4977-4982.
39. Rao AD, Rashid AS, Chen Q, Rosangela C Villar, Daria Kobyzeva, et al. (2017) Reirradiation for recurrent pediatric central nervous system malignancies: a multi-institutional review. Int J Radiat Oncol Biol Phys 99: 634-641.
40. Tejpal Gupta, Madan Maitre, Goda Jayant Sastri, Rahul Krishnatry, Neelam Shirsat, et al. (2019) Outcomes of salvage re-irradiation in recurrent medulloblastoma correlate with age at initial diagnosis, primary risk-stratification, and molecular subgrouping. Journal of Neuro-Oncology 144: 283-291.
41. Padovani L, Andre N, Gentet JC, Dominique Figarella Branger, Didier Scavarda, et al. (2011) Reirradiation and concomitant metronomic temozolomide: an efficient combination for local control in medulloblastoma disease? J Pediatr Hematol Oncol 33: 600-604.
42. Dufour C, Beaugrand A, Pizer B, Julie Micheli, Marie-Stephanie Aubelle, et al. (2012) Metastatic medulloblastoma in childhood: Chang's classification revisited. Int J Surg Oncol 2012: 245385.
43. Wei RL, Nguyen ST, Yang JN, Wolff J, Mahajan A (2012) Salvage craniospinal irradiation with an intensity modulated radiotherapy technique for patients with disseminated neuraxis disease. Pract Radiat Oncol 2: e69-75.
44. Wetmore C, Herington D, Lin T, Onar-Thomas A, Gajjar A, et al. (2014) Reirradiation of recurrent medulloblastoma: does clinical benefit outweigh risk for toxicity? Cancer 120: 3731-3737.
45. Fleischhack G, Reif S, Hasan C, Jaehde U, Hettmer S, et al. (2001) Feasibility of intraventricular administration of etoposide in patients with metastatic brain tumours. Br J Cancer 84: 1453-1459.
46. Chamberlain MC (1997) Pediatric leptomeningeal metastases: outcome following combined therapy. J Child Neurol 12: 53-59.
47. Waki F, Ando M, Takashima A, Yonemori K, Nokihara H, et al. (2009) Prognostic factors and clinical outcomes in patients with leptomeningeal metastasis from solid tumors. J Neurooncol 93: 205-212.
48. Ruggiero A, Conter V, Milani M, Biagi E, Lazzareschi I, et al. (2001) Intrathecal chemotherapy with antineoplastic agents in children. Paediatr Drugs 3: 237-246.
49. Siegal T, Lossos A, Pfeffer MR (1994) Leptomeningeal metastases: analysis of 31 patients with sustained off-therapy response following combined-modality therapy. Neurology 44: 1463-1469.
50. Grahn JA, Parkinson JA, Owen AM (2008) The cognitive functions of the caudate nucleus. Prog Neurobiol 86: 141-155.
51. Fisher HE, Aron A, Brown LL (2006) Romantic love: a mammalian brain system for mate choice. Philos Trans R Soc Lond B Biol Sci 361: 2173-2186.
52. Williams R, Cresswell F, McClure M, Lane R (2011) Creutzfeldt-jakob disease as a cause of cognitive decline and seizures in the elderly: diagnostic pointers and strategy for investigation. Case Rep Med 2011: 719583.