in vivo *34*: 1283-1288 (2020)
doi:10.21873/invivo.11903

Salvage Re-irradiation Options in Adult Medulloblastoma: A Case Report and Review of the Literature

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Abstract. *Background/Aim: Medulloblastoma is a rare tumor of adult age, while it occurs more frequently in children. Given the rarity, there is a lack of evidence for the treatment of recurrent disease. Few data are available about salvage re-irradiation collecting very heterogeneous series. Case Report: A 51-year-old male presented with headache, nausea, double vision, and gait disorders. A contrast-enhanced brain-MRI showed the presence of multifocal medulloblastoma. After surgery, adjuvant craniospinal radiotherapy was performed, chemotherapy was stopped due to toxicity. After 27 months, a new MRI and a Methionine-PET revealed a late pontocerebellar relapse; multidisciplinary board decided for a SBRT treatment. The second course of RT was well tolerated and 14 months later, the patient is alive in good general conditions, with no evidence of disease. Conclusion: Our experience supports the use of salvage stereotactic radiotherapy as a safe and effective treatment option.*

Medulloblastoma is one of the most common central nervous system tumors of childhood (1), while it has an extremely lower incidence in the adult age, particularly in >40 years patients (2). Furthermore, in older patients it may occur with unusual presentations, like multifocal disease, of which only six cases are described in the literature (3-8). Due to its rarity in the older population, pre-operative diagnosis may be challenging since radiological features may differ from pediatric cases, for example in terms of lower contrast enhancement (9). Standard treatments for children are usually based on the multimodal combination of surgery plus adjuvant craniospinal radiotherapy with or without chemotherapy (10, 11).

The extremely rare incidence of medulloblastoma in adult patients renders the therapeutic management of this subset of individuals difficult, with most evidence coming from the adoption of pediatric guidelines that support the role of post-operative chemo-radiation to improve overall survival (12). Actually, for adult patients, the upfront use of chemotherapy is controversial, with many reports suggesting a higher incidence of toxicity in older subjects compared to children (13). Recent molecular analyses provided new data to stratify all medulloblastoma patients in four different subgroups (WNT, SH, group 3 and 4) with different prognosis, although the impact on therapeutic strategy is still limited (14). Moreover, unlike younger patients, adult medulloblastomas have a higher incidence of late relapses, that are usually associated with a poorer prognosis, since there are not enough evidence to recommend a standardized therapeutic approach, that currently may include as alternatives re-resection or re-irradiation or high-dose chemotherapy followed by stem cell transplantation (15, 16).

Case Report

In 2016, a 51-year-old male presented at our Center after the recent onset of headache, nausea, double vision, slurred speech, and gait disorders. A contrast-enhanced brain-MRI showed the presence of two cerebellar lesions close to the cerebellar tonsils and vermis (Figure 1).

Subsequently, a right tonsillectomy with a sub-occipital median approach in neuronavigation was performed.

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Key Words: Medulloblastoma, re-irradiation, adult patients.

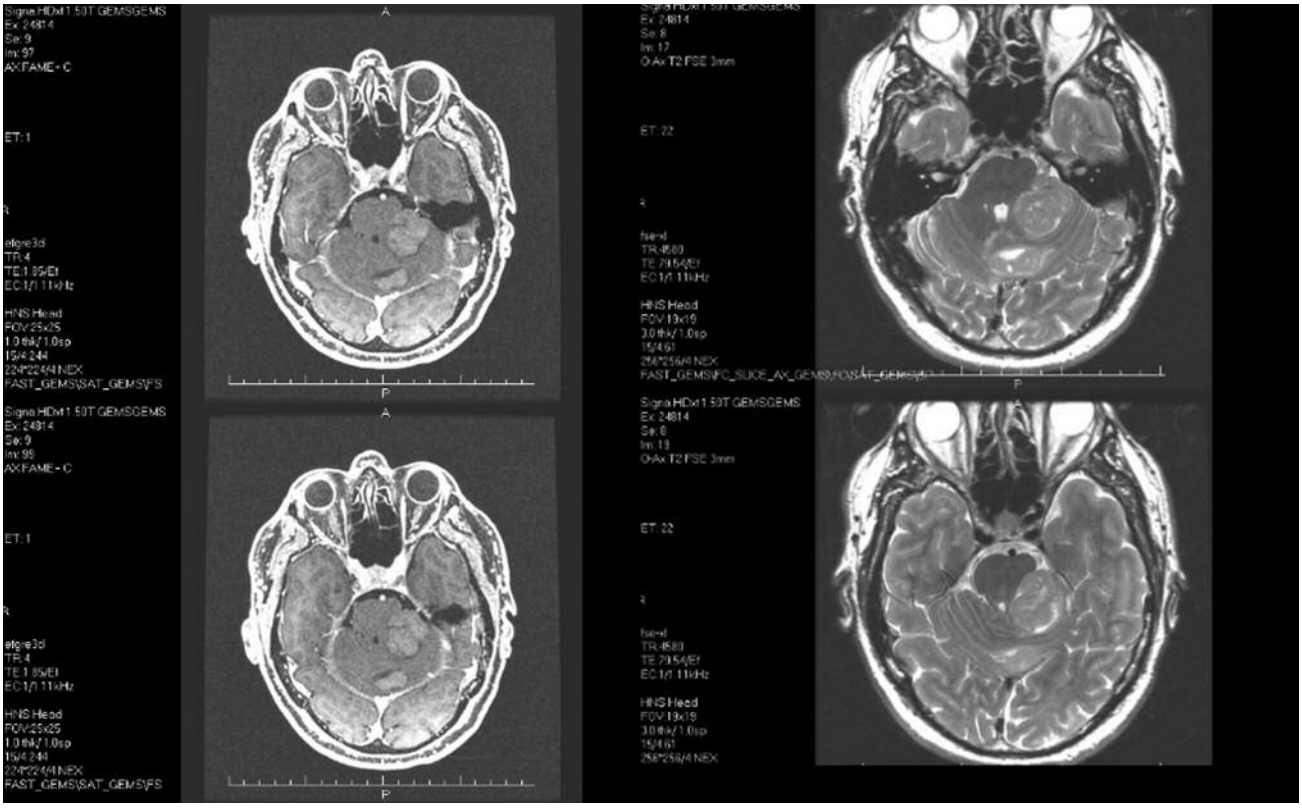

Figure 1. *Preoperative brain MRI in T1-weighted contrast enhanced (right) and T2-weighted (left) sequence.*

Cerebrospinal fluid cytology examination was negative, and a spine-MRI with contrast reported several hyperintense areas in the T2-weighted sequence with radiological features suspected for multifocal neoplastic disease. Histology examination was positive for classic-type medulloblastoma MIB1=20%. No molecular profiling was performed. A multidisciplinary board decided for adjuvant chemo-radiation and the patient underwent craniospinal RT for a total dose of 36 Gy in conventional fractionation plus a sequential boost to posterior fossa for a total dose of 54 Gy. Radiotherapy treatment was performed using Helical Tomotherapy using a thermoplastic mask for immobilization and daily megavoltage CT scan imaging before each fraction. Then, the patient interrupted the planned chemotherapy regimen (CDDP+CCNU+vincristine) after one cycle due to renal toxicity. Follow-up was negative until November 2018, when a brain-MRI reported the presence of a contrast enhanced area in the left cerebello-pontine angle suspected for relapsed disease (Figure 2). This finding was also reported by a Methionine-PET scan that confirmed the presence of an area of pathological uptake. Subsequently, after 27 months from the first treatment, the patient underwent stereotactic hypofractionated radiotherapy to the site of relapse for a total dose of 30 Gy in 5 fractions by means of Helical Tomotherapy. Target volume delineation was performed through MRI-Methionine PET-image fusion, applying to the gross tumor volume (GTV) a 3-mm margin overlapping the brainstem, which was given a higher priority during the planning phase. Treatment was well tolerated, with no observed acute or late toxicity. No other therapies were administered. After 14 months a contrast-enhanced brain-MRI reported no evidence of disease, the patient is alive and in good general conditions. Informed consent was obtained before the start of all the treatment.

Discussion

Currently, a standard treatment strategy for recurrent medulloblastoma is not yet defined and different options may be considered: maximal safe resection where suitable, or radiotherapy with or without chemotherapy, or high-dose chemotherapy followed by autologous stem cell transplantation.

External-beam radiotherapy can be offered either in a definitive setting or after maximal safe resection, despite most of the literature reports data concerning exclusive intent. To date, almost 300 cases of re-irradiation after craniospinal radiotherapy are reported in the literature (Table I), but it is hard to compare these data due to the heterogeneity of the

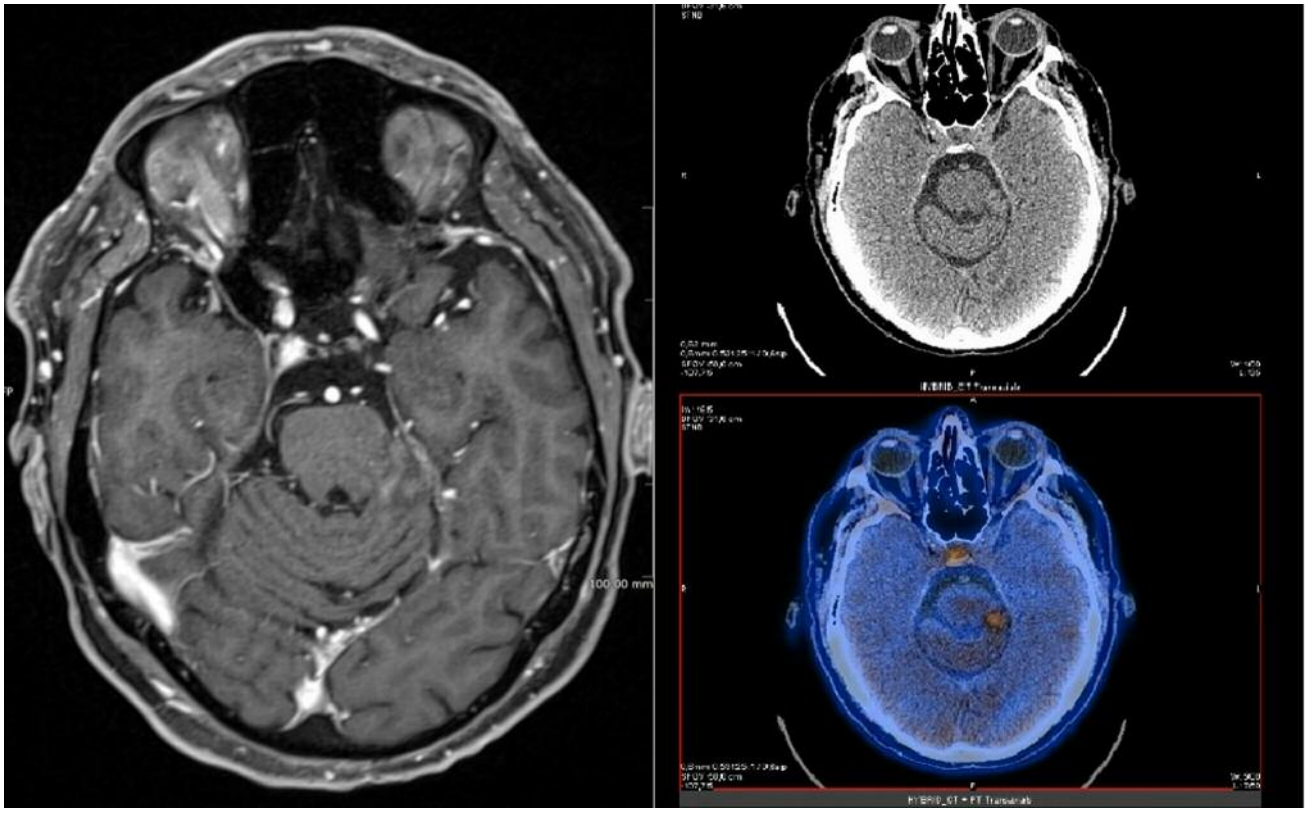

Figure 2. *Brain MRI in T1-weighted contrast enhanced before stereotactic radiotherapy (left) and after 14 months (right).*

cohorts; furthermore, different RT schedules are used with or without chemotherapy, and only a few reports are available on the use of stereotactic radiotherapy (17-32).

The main concern of re-treatment is the higher risk of toxicity, in particular for brain radionecrosis (33, 34). Radiobiological studies have described a reduced risk of normal brain radionecrosis when the normalized total dose is lower than 100 Gy, suggesting that tumor diameter, performance status, concurrent chemotherapy and time between the two courses of radiotherapy may be associated to an increased risk of neurotoxicity (35).

Similarly to the spinal cord, animal model studies revealed that the normal brain may recover up to 50% within the first 2 years from initial treatment if doses below tolerance have been delivered (36). In this scenario, when proposing a re-irradiation, the choice of the fractionation regimen is often driven by the presentation of the recurrent disease: while local small relapses may benefit from a focal treatment, like stereotactic radiotherapy, that combines higher therapeutic doses with a lower normal brain exposure, a recurrent larger or disseminated tumor may benefit from less aggressive RT schedules, like conventional or hyperfractionated regimens, that still allow safe delivery of a tumoricidal dose with an acceptable risk of late neurotoxicity.

The evaluation of all these factors focus the need for a careful patient selection process; this is also confirmed by a recent series published by Gupta *et al*. concerning 28 patients with relapsed medulloblastoma who underwent salvage re-irradiation, performed either with re-craniospinal RT or with focal treatments both in conventional or hyperfractionated regimens (32). The authors reported an acceptable profile of toxicity, describing only one case of symptomatic late radionecrosis after re-craniospinal irradiation.

Bakst *et al*. also adopted conventional schedules for the re-treatment of 13 patients with relapsed medulloblastoma, collecting 5-years progression-free survival and overall survival of 48% and 65%, respectively, with only one case of radiological in-field brain radionecrosis. The authors also observed better outcomes in patients with no evidence of disease after re-surgical excision, compared to non-surgical cases (29).

The potential advantage of hypofractionation or radiosurgery lies in the possibility to improve local control rates in patients with macroscopic disease, providing more precise irradiation of a small area, with steep dose gradients that may lead to a lower exposure of nearby healthy structures. The use of stereotactic radiosurgery is favorably reported by Napieralska *et al*. in a series of 14 patients

Table I. *Literature studies of salvage RT after craniospinal irradiation.*

Authors	N° of patients	Time to Re-RT (years)	Site of relapse	Radiotherapy schedule	Salvage RT toxicity	Clinical outcomes
Privitera *et al.* (17)	1	6	Brainstem and SC	Total dose=24 Gy	No toxicity	Death by disease after 35 months from re-RT
Rao *et al.* (18)	67 (20 medulloblastoma)	2 (0.3-16.5)	NR	Median EQD2=63.7 Gy (4 SRS, 4 protons, 1 BRT, 1 2DRT, 3 combined modality 46 IMRT, 9 3DCRT)	1 radiological RN	Median OS=8.4 months
Wetmore *et al.* (19)	14	3.9 (0.8-8.9)	6 PF, 4 LS, 2 VS, 1 SC	36 Gy/1.8 Gy/fx	Increased risk of neurotoxicity compared to a no-RT cohort	5-year OS=55%
Buglione *et al.* (20)	1	8	Right cerebellum	52.8 Gy/1.2 Gy/fx BID	No toxicity	Local and distant relapse after 10 months
Keshavarzi *et al.* (21)	1	NR	NR	14 Gy SRS	No toxicity	Alive after 12 months
Cieslak *et al.* (22)	1	23	Right cerebellar lobe	45 Gy/1.8 Gy/fx	No toxicity	Alive after 15 months
Padovani *et al.* (23)	5	6	3 PF, 1 SC, 1 FL	20-36 Gy/1.8 Gy/fx	No toxicity	80% alive after mean follow-up of 24 months
Saran *et al.* (24)	14	3 (1-18)	PF	30-40 Gy/5 Gy/fx	No toxicity	5-year OS=20%
Patrice *et al.* (25)	14	1.6 (0.08-8.08)	PF	12 Gy SRS	No toxicity	2-year OS=45%
Abe *et al.* (26)	12 (18 lesions)	1.29 (0.5-4)	4 PF 14 mets	8→20 Gy SRS 10→17 Gy/8.5 Gy/fx	1 G3 brain edema	3-year OS=25%
Milker-Zabel *et al.* (27)	29	2.75 (0.1-7.38)	NR	21→24 Gy/1.8-7.5 Gy/fx 8→15 Gy SRS	No toxicity	6-year OS=35%
Chojnacka *et al.* (28)	6	3.25 (0.4-4.25)	3 PF, 2 FL, 1 occipital lobe	40 Gy/2 Gy/fx	4 G2 nausea, no G≥3	Median OS= 17.5 months
Bakst *et al.* (29)	14	4.75 (2.1-9.3)	62% PF; 31% supratentorial; 38% SC	30 Gy/1.5 Gy/fx	1 radiological RN	5-year OS=65%
Massimino *et al.* (30)	10	1.9 (1.4-5.75)	1 PF, 7 LS, 2 cerebral cortex	7→20 Gy/1.3 Gy/fx BID (re-CSI) 3→Total dose= 50 Gy	NR	5-year OS=20%
Napieralska *et al.* (31)	14	1.3 (0.25-6.5)	5 FL, 5 PF, 2 TL, 1 PL, 1 cribriform plate	12→6-15 Gy SRS 1→15 Gy/5Gy/fx 1→30 Gy/5Gy/fx	7 G2 brain edema	2-year OS=70%
Gupta *et al.* (32)	28	4.08 (1-8.1)	NR	7→36 Gy/ 1Gy/fx (re-CSI) 21→42.5 Gy/1.8 Gy/fx	1 symptomatic RN	2-year OS=51%
Our experience	1	2	Left CPA	30 Gy/5 Gy/fx	No toxicity	Alive after 14 months

2DRT: 2-Dimensional radiotherapy; 3DCRT: 3-dimensional conformal therapy; BID: bis in die; BRT: brachytherapy; CPA: cerebello-pontine angle; CSI: craniospinal irradiation; FL: frontal lobe; IMRT: intensity modulated radiotherapy; LS: leptomeningeal spread; NR: not reported; OS: overall survival; PF: posterior fossa; PL: parietal lobe; RN: radionecrosis; SC: spinal cord; SRS: stereotactic radiosurgery; TL: temporal lobe; VS: ventricular system.

treated with a median dose of 15 Gy in single or in three fractions, with no evidence of brain necrosis and promising results in terms of clinical outcomes (31).

Similar data are reported by Abe *et al.*, in a series of 12 adult and pediatric patients treated with stereotactic radiotherapy plus chemotherapy. The authors observed one case of brainstem edema and the patient died after 14 months for tumor dissemination; moreover, two patients developed respectively multiple organ failure and bulbar palsy due to chemotherapy (26). Despite the potential higher risk of metastatic spread, the

combination of radio- and chemotherapy must be carefully evaluated in the recurrent setting, especially for adult patients who are more likely to have relevant toxicity given by systemic treatment (13).

Given the excellent performance status of our patient and the long interval of 27 months from the previous craniospinal RT, in our experience we decided to propose stereotactic radiotherapy to the cerebello-pontine angle relapse with the aim to provide a radical treatment to a smaller volume, in order to minimize the risk of toxicity, as also reported by other authors (37).

Concerning chemotherapy, the multidisciplinary board decided not to perform a systemic therapy, due to the high toxicity experienced during the first cycle and the patient was managed solely with stereotactic radiotherapy. The second course of RT was well tolerated, with no relevant side-effects, and after 14 months he is alive and in good general conditions, with no evidence of disease.

Re-irradiation of central nervous system tumors has become of increasing interest since the constant progress of both imaging and radiation technology is leading to a highly accurate targeting of tumor volumes, improving the possibility of a better organ-at-risk sparing. Given the rarity of the disease, especially in adult patients, when proposing re-irradiation, the concern for brain toxicity must be carefully assessed to provide a maximum tailored approach.

To date, literature evidence concerning salvage radiotherapy for relapsed medulloblastoma is scarce and based on heterogeneous series that include both pediatric and adult patients, applying wide different treatment regimens. Our experience reports an unusual presentation of adult medulloblastoma and supports the use of salvage stereotactic radiotherapy for a locally relapsed disease showing excellent results both in terms of safety and clinical outcomes, despite a longer follow up is needed.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

Manuscript drafting: Francesco Cuccia, Gianluca Mortellaro, Giuseppe Craparo; Literature research: Francesco Cuccia, Lucia Ognibene; Conception and final revision: Giuseppe Ferrera, Antonio Lo Casto.

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Received January 2, 2020
Revised January 25, 2020
Accepted January 29, 2020