

# 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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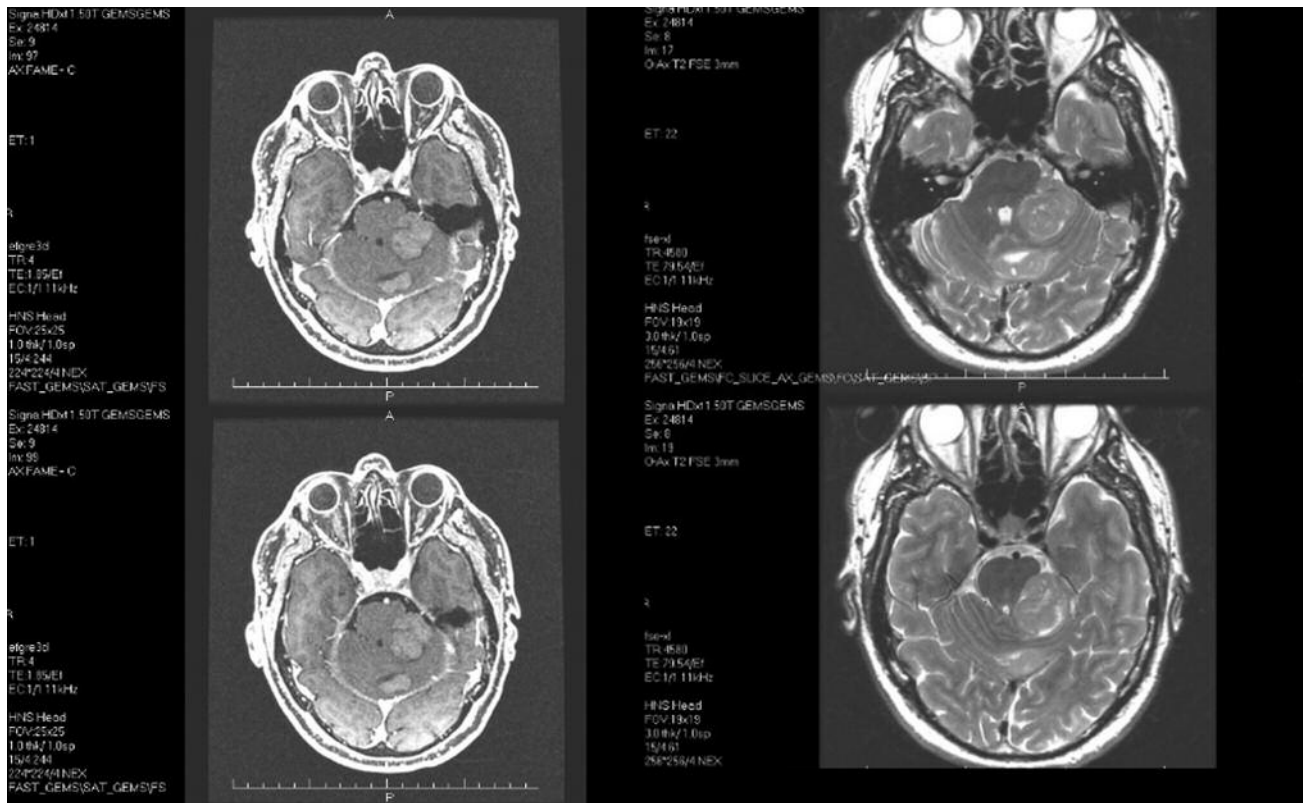


Figure 1. Preoperative brain MRI in T1-weighted contrast enhanced (right) and T2-weighted (left) sequence.

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

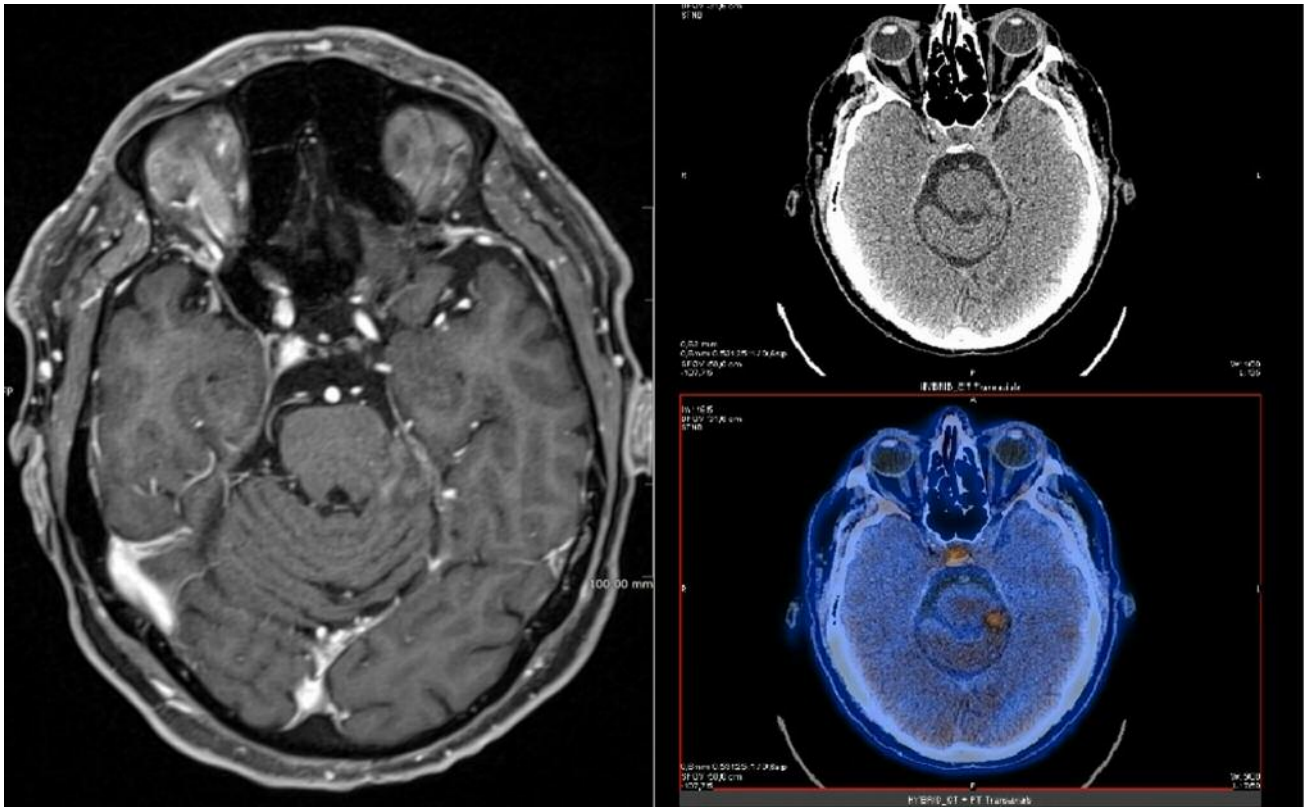


Figure 2. Brain MRI in T1-weighted contrast enhanced before stereotactic radiotherapy (left) and after 14 months (right).

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 <i>et al.</i> (17)	1	6	Brainstem and SC	Total dose=24 Gy	No toxicity	Death by disease after 35 months from re-RT
Rao <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (20)	1	8	Right cerebellum	52.8 Gy/1.2 Gy/fx BID	No toxicity	Local and distant relapse after 10 months
Keshavarzi <i>et al.</i> (21)	1	NR	NR	14 Gy SRS	No toxicity	Alive after 12 months
Cieslak <i>et al.</i> (22)	1	23	Right cerebellar lobe	45 Gy/1.8 Gy/fx	No toxicity	Alive after 15 months
Padovani <i>et al.</i> (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 <i>et al.</i> (24)	14	3 (1-18)	PF	30-40 Gy/5 Gy/fx	No toxicity	5-year OS=20%
Patrice <i>et al.</i> (25)	14	1.6 (0.08-8.08)	PF	12 Gy SRS	No toxicity	2-year OS=45%
Abe <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (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 <i>et al.</i> (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.

## References

- Farwell JR, Dohrmann GJ and Flannery JT: Medulloblastoma in childhood: an epidemiological study. *J Neurosurg* 61(4): 657-664, 1984. PMID: 6470775. DOI: 10.3171/jns.1984.61.4.657
- Balducci M, Chiesa S, Chieffo D, Manfrida S, Dinapoli N, Fiorentino A, Miccichè F, Frascino V, Anile C, Valentini V and De Bari B: The role of radiotherapy in adult medulloblastoma: long-term single-institution experience and a review of the literature. *J Neurooncol* 106(2): 315-323, 2012. PMID: 21805324. DOI: 10.1007/s11060-011-0665-7
- Gliemroth J, Kehler U, Knopp U, Reusche E and Nowak G: A multifocal cerebellar and supratentorial medulloblastoma in an adult. *Acta Neurochir (Wien)* 140(7): 723-724, 1998. PMID: 9781288. DOI: 10.1007/s007010050169
- Spagnoli D, Tomei G, Masini B, De Santis A, Grimoldi N, Lucarini C and Gaini SM: A case of multifocal cerebellar medulloblastoma in an adult patient. *J Neurosurg Sci* 34(3-4): 323-325, 1990. PMID: 2098514.
- Shen WC and Yang CF: Multifocal cerebellar medulloblastoma: CT findings. *J Comput Assist Tomogr* 12(5): 894, 1988. PMID: 3170856. DOI: 10.1097/00004728-198809010-00037
- Balik V, Trojanec R, Holzerova M, Tuckova L, Sulla I, Megova M, Vaverka M, Hrabalek L and Ehrmann J: An adult multifocal medulloblastoma with diffuse acute postoperative cerebellar swelling: immunohistochemical and molecular genetics analysis. *Neurosurg Rev* 38(1): 1-10; discussion 10, 2015. PMID: 24913771. DOI: 10.1007/s10143-014-0556-4
- Saad AG, Balik V, Parvez A and El Jamal SM: Multifocal supra and infratentorial medulloblastoma in an adult: Histologic, immunohistochemical, and molecular evaluation of a rare case and review of the literature. *Appl Immunohistochem Mol Morphol* 25(10): e89-e94, 2017. PMID: 27801730. DOI: 10.1097/PAI.0000000000000447
- Hernández Cancela RM, Pombo Otero J and Concha-Lopez A: A case of multifocal medulloblastoma in an adult patient. *Rev Esp Patol* 50(1): 45-48, 2017. PMID: 29179964. DOI: 10.1016/j.patol.2015.12.005
- Ciccarino P, Rotilio A, Rossetto M, Manara R, Orvieto E, Berti F, Lombardi G, d'Avella D, Scienza R and Della Puppa A: Multifocal presentation of medulloblastoma in adulthood. *J Neurooncol* 107(2): 233-237, 2012. PMID: 22071791. DOI:10.1007/s11060-011-0746-7
- Anagnostopoulos AK, Papathanassiou C, Karamolegou K, Anastasiadou E, Dimas KS, Kontos H, Koutsopoulos A, Prodromou N, Tzortzatou-Stathopoulou F and Tsangaris GT: Proteomic studies of pediatric medulloblastoma tumors with 17p deletion. *J Proteome Res* 14(2): 1076-1088, 2015. PMID: 25543836. DOI: 10.1021/pr501219f
- Tsangaris GT, Dimas K, Malamou A, Katsafadou A, Papathanasiou C, Stravopodis DJ, Vorgias CE, Gazouli M and Anagnostopoulos AK: Molecular proteomic characterization of a pediatric medulloblastoma xenograft. *Cancer Genomics Proteomics* 14(4): 267-275, 2017. PMID: 28647700. DOI: 10.21873/cgp.20037
- Majd N and Penas-Prado M: Updates on management of adult medulloblastoma. *Curr Treat Options Oncol* 20(8): 64, 2019. PMID: 31236711. DOI: 10.1007/s11864-019-0663-0
- Beier D, Proescholdt M, Reinert C, Pietsch T, Jones DTW, Pfister SM, Hattingen E, Seidel C, Dirven L, Luerding R, Reijneveld J, Warmuth-Metz M, Bonsanto M, Bremer M, Combs SE, Rieken S, Herrlinger U, Kuntze H, Mayer-Steinacker R, Moskopp D, Schneider T, Beringer A, Schlegel U, Stummer W, Welker H, Weyerbrock A, Paulsen F, Rutkowski S, Weller M, Wick W, Kortmann RD, Bogdahn U and Hau P: Multicenter pilot study of radiochemotherapy as first-line treatment for adults with medulloblastoma (NOA-07). *Neuro Oncol* 20(3): 400-410, 2018. PMID: 29016837. DOI: 10.1093/neuonc/nox155

- 14 Buglione M, Ghirardelli P, Triggiani L, Pedretti S, Pasinetti N, De Bari B, Tonoli S, Borghetti P, Spiazzi L and Magrini SM: Radiotherapy for adult medulloblastoma: Long term result from a single institution. A review of prognostic factors and why we do need a multi-institutional cooperative program. *Rep Pract Oncol Radiother* 20(4): 284-291, 2015. PMID: 26109916. DOI: 10.1016/j.rpor.2015.03.003
- 15 Brandes AA, Franceschi E, Tosoni A, Blatt V and Ermani M: Long-term results of a prospective study on the treatment of medulloblastoma in adults. *Cancer* 110(9): 2035-2041, 2007. PMID: 17823910. DOI: 10.1002/cncr.23003
- 16 Herlinger U, Steinbrecher A, Rieger J, Hau P, Kortmann RD, Meyermann R, Schabet M, Bamberg M, Dichgans J, Bogdahn U and Weller M: Adult medulloblastoma: prognostic factors and response to therapy at diagnosis and at relapse. *J Neurol* 252(3): 291-299, 2005. PMID: 16189725. DOI: 10.1007/s00415-005-0560-2
- 17 Privitera G, Acquaviva G, Ettore GC and Spatola C: Antiangiogenic therapy in the treatment of recurrent medulloblastoma in the adult: case report and review of the literature. *J Oncol* 2009: 247873, 2009. PMID: 20111585. DOI: 10.1155/2009/247873
- 18 Rao AD, Rashid AS, Chen Q, Villar RC, Kobzyeva D, Nilsson K, Dieckmann K, Nechesnyuk A, Ermoian R, Alcorn S, MacDonald SM, Ladra MM, Ford EC, Winey BA, Figueiredo MLS, Chen MJ and Terezakis SA: Reirradiation for recurrent pediatric central nervous system malignancies: A multi-institutional review. *Int J Radiat Oncol Biol Phys* 99(3): 634-641, 2017. PMID: 29280457. DOI: 10.1016/j.ijrobp.2017.07.026
- 19 Wetmore C, Herington D, Lin T, Onar-Thomas A, Gajjar A and Merchant TE: Reirradiation of recurrent medulloblastoma: does clinical benefit outweigh risk for toxicity? *Cancer* 120(23): 3731-3737, 2014. PMID: 25080363. DOI: 10.1002/cncr.28907
- 20 Buglione M, Triggiani L, Grisanti S, Liserre R, Buttolo L, Gipponi S, Bonetti F, Todeschini A, Spiazzi L and Magrini SM: Retreatment of recurrent adult medulloblastoma with radiotherapy: a case report and review of the literature. *J Med Case Rep* 7: 64, 2013. PMID: 23497715. DOI: 10.1186/1752-1947-7-64
- 21 Keshavarzi S, Meltzer H, Ben-Haim S, Newman CB, Lawson JD, Levy ML and Murphy K: Initial clinical experience with frameless optically guided stereotactic radiosurgery/radiotherapy in pediatric patients. *Childs Nerv Syst* 25(7): 837-844, 2009. PMID: 19326128. DOI: 10.1007/s00381-009-0840-8
- 22 Cieślak E, Kepka L, Fijuth J, Marchel A and Kroh H: Very late relapse of medulloblastoma. *Folia Neuropathol* 42(1): 49-53, 2004. PMID: 15119746.
- 23 Padovani L, Andre N, Gentet JC, Figarella Branger D, Scavarda D, Verschuur A, Chinot O, Cowen D and Muracciole X: Reirradiation and concomitant metronomic temozolomide: an efficient combination for local control in medulloblastoma disease? *J Pediatr Hematol Oncol* 33(8): 600-604, 2011. PMID: 22042276. DOI: 10.1097/MPH.0b013e3182331eaf
- 24 Saran F, Baumert BG, Creak AL, Warrington AP, Ashley S, Traish D and Brada M: Hypofractionated stereotactic radiotherapy in the management of recurrent or residual medulloblastoma/PNET. *Pediatr Blood Cancer* 50(3): 554-560, 2008. PMID: 17941071. DOI: 10.1002/pbc.21382
- 25 Patrice SJ, Tarbell NJ, Goumnerova LC, Shrieve DC, Black PM and Loeffler JS: Results of radiosurgery in the management of recurrent and residual medulloblastoma. *Pediatr Neurosurg* 22(4): 197-203, 1995. PMID: 7619720. DOI: 10.1159/000120901
- 26 Abe M, Tokumaru S, Tabuchi K, Kida Y, Takagi M and Imamura J: Stereotactic radiation therapy with chemotherapy in the management of recurrent medulloblastomas. *Pediatr Neurosurg* 42(2): 81-88, 2006. PMID: 16465076. DOI: 10.1159/000090460
- 27 Milker-Zabel S, Zabel A, Thilmann C, Zuna I, Hoess A, Wannemacher M and Debus J: Results of three-dimensional stereotactically-guided radiotherapy in recurrent medulloblastoma. *J Neurooncol* 60(3): 227-233, 2002. PMID: 12510774. DOI: 10.1023/a:1021184400053
- 28 Chojnacka M, Skowrońska-Gardas A, Pędziwiatr K, Morawska-Kaczyńska M, Perek M and Perek D: Reirradiation of relapsed brain tumors in children. *Rep Pract Oncol Radiother* 17(1): 32-37, 2011. PMID: 24376994. DOI: 10.1016/j.rpor.2011.10.004
- 29 Bakst RL, Dunkel IJ, Gilheeney S, Khakoo Y, Becher O, Souweidane MM and Wolden SL: Reirradiation for recurrent medulloblastoma. *Cancer* 117(21): 4977-4982, 2011. PMID: 21495027. DOI: 10.1002/cncr.26148
- 30 Massimino M, Gandola L, Spreafico F, Biassoni V, Luksch R, Collini P, Solero CN, Simonetti F, Pignoli E, Cefalo G, Poggi G, Modena P, Mariani L, Potepan P, Podda M, Casanova M, Pecori E, Acerno S, Ferrari A, Terenziani M, Meazza C, Polastri D, Ravagnani F and Fossati-Bellani F: No salvage using high-dose chemotherapy plus/minus reirradiation for relapsing previously irradiated medulloblastoma. *Int J Radiat Oncol Biol Phys* 73(5): 1358-1363, 2009. PMID: 19019566. DOI: 10.1016/j.ijrobp.2008.06.1930
- 31 Napieralska A, Brąclik I, Radwan M, Mandera M and Blamek S: Radiosurgery or hypofractionated stereotactic radiotherapy after craniospinal irradiation in children and adults with medulloblastoma and ependymoma. *Childs Nerv Syst* 35(2): 267-275, 2019. PMID: 30515559. DOI: 10.1007/s00381-018-4010-8
- 32 Gupta T, Maitre M, Sastri GJ, Krishnatry R, Shirsat N, Epari S, Sahay A, Chinnaswamy G, Patil V, Shetty P and Moiyadi A: Outcomes of salvage re-irradiation in recurrent medulloblastoma correlate with age at initial diagnosis, primary risk-stratification, and molecular subgrouping. *J Neurooncol* 144(2): 283-291, 2019. PMID: 31236820. DOI: 10.1007/s11060-019-03225-9
- 33 Bauman GS, Sneed PK, Wara WM, Stalpers LJ, Chang SM, McDermott MW, Gutin PH and Larson DA: Reirradiation of primary CNS tumors. *Int J Radiat Oncol Biol Phys* 36(2): 433-441, 1996. PMID: 8892469. DOI: 10.1016/s0360-3016(96)00315-x
- 34 Marks JE, Baglan RJ, Prassad SC and Blank WF: Cerebral radionecrosis: incidence and risk in relation to dose, time, fractionation and volume. *Int J Radiat Oncol Biol Phys* 7(2): 243-252, 1981. PMID: 6260715. DOI: 10.1016/0360-3016(81)90443-0
- 35 Mayer R and Sminia P: Reirradiation tolerance of the human brain. *Int J Radiat Oncol Biol Phys* 70(5): 1350-1360, 2008. PMID: 18037587. DOI: 10.1016/j.ijrobp.2007.08.015
- 36 Withers HR: Biologic basis for altered fractionation schemes. *Cancer* 55(9 Suppl): 2086-2095, 1985. PMID: 3919923. DOI: 10.1002/1097-0142(19850501)55:9+<2086::aid-cncr2820551409>3.0.co;2-1
- 37 Nieder C, Andratschke NH and Grosu AL: Re-irradiation for recurrent primary brain tumors. *Anticancer Res* 36(10): 4985-4995, 2016. PMID: 27798857. DOI: 10.21873/anticancer.11067

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