ISSN 2689-8268 | Volume 4

American Journal of Surgery and Clinical Case Reports

Case Report Open Access

The Importance of Re-Surgery with Cranio-Spinal Re-Irradiation in Children with Late Local Medulloblastoma Recurrence - Clinical Case with A Literature Review

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Received: 12 Apr 2022
Accepted: 06 May 2022
Published: 11 May 2022
J Short Name: AJSCCR

Citation:

Lena Marinova. The Importance of Re-Surgery with Cranio-Spinal Re-Irradiation in Children with Late Local Medulloblastoma Recurrence - Clinical Case with A Literature Review. Ame J Surg Clin Case Rep. 2022; 4(14): 1-5

Keywords:

Medulloblastoma; Local recurrence; Re-surgery; Cranio-spinal re-irradiation; Complex treatment

1. Abstract

Medulloblastoma (MB) is the most common malignant brain tumour in children. Despite the complex therapy, including a visible total surgery, cranio-spinal radiotherapy (CSRT) with boost in tumor bed and adjuvant chemotherapy (Ch), there are late local recurrences with poor prognosis. We present a 9-year old boy with local medulloblastoma recurrence three years after subtotal tumor resection, CSRT and Ch. The objective of the article is to highlight the importance of total re-surgery with subsequent cranio-spinal re-irradiation with tumor bed boost in children with late local medulloblastoma recurrence. In disease progression, regardless of recurrence, local or metastatic in cranio-spinal axis, the combination of the two local methods re-surgery followed by re-irradiation improve the outcome of recurrent MB children.

2. Introduction

Medulloblastoma (MB) is the most common malignant brain tumour in children [1]. The big healing advances came in the 1970s, when megavolt radiotherapy (RT) with prophylactic spinal irradiation was added to the treatment regimen, and 5-year survival rates reached 60% [2-4]. Relapses occur in approximately 30% of patients and are almost always fatal [5-7]. Improved survival rates were observed by increasing the RT dose to the posterior cranial fossa [8]. The 5-year progression free survival (PFS) for MB, the most common childhood malignant brain tumour, is now expected to be 70–80% in the 'standard' or 'average' risk subgroup [9]. In 1984, Barrer et al. [10] reviewed re-surgery of recurrent brain tumors and concluded that this intervention is "a useful therapy prolonging both quality and quantity of life." Only reoperation can significantly prolong survival time, and therefore, early reoperation can be considered to improve the outcome of children with recurrent MB [11]. We present a late second local recurrence at a twelve-year-old boy of desmoplastic medulloblastoma, three years after subtotal surgery, cranio-spinal radiotherapy (CSRT) and chemotherapy (Ch).

3. Clinical Case

We present a 9-year old boy with a complaint of nausea, vomiting and fatigue. After the brain CT, a tumor in the small brain was diagnosed. From MRT /27.10.2018- In the fourth brain ventricle, a large soft tumor with a heterogeneous structure and axial dimensions 43/40 mm with significantly increased intensity after intravenous contrast and with pons and medulla oblongata compression, was visualized. On 31.10.2018, subtotal tumor resection, due to intraoperative complication tachycardia was carried out. Intraoperatively a well-vascularized tumor, originating in the cerebellum vermis, entering and filling the fourth ventricle and prominent through the right foramen of Luschka, was visualized. A visibly total tumor resection with histological result desmoplastic medulloblastoma was performed. On MRT/ 20.11.18 residual tumor formation at the rear-left surface of the pons and left minor hemisphere measuring 10/8.8 mm, which is hyperintense in T2 and T2 FLAIR, was detected. The child was targeted for intensity modulated craniospinal radiotherapy (CSRT) up to total dose (TD) 23.4 Gy with a tumor bed boost up to TD 54 Gy, conducted for the period 17.12.2018- 05.02.2019 (Figure 1**).** From 07.03.2019 to 24.01.2020 8 courses adjuvant chemotherapy (Ch) were conducted. After four courses Ch, the control MRT / July 2019 reported a residual lesion measuring 4.5 mm without perifocal edema (Figure 2). After Ch completion, disease remission was established. After

half a year, MRT on 26.01.2021 visualised the first local recurrence in the fourth brain ventricle measuring 5/7 mm and caudally another lesion measuring 4/4.5 mm. In February 2021, non-radical tumor extirpation with a histological result recurrence of medulloblastoma was performed. The child continues Ch under the HIT Med Guidance Protocol 2017. After 6 months, MRT reported a second inoperable local recurrence (Figure 3). We are currently conducting Intensity Modulated Craniospinal Re- irradiation with VMAT method with daily dose (DD) 1,5 Gy up to TD 23.4 Gy with a simultaneous boost in posterior cranial fossa with DD 1,8 Gy up to TD 30.5 Gy, as well as in the tumor bed with DD 2 Gy up to TD 34 Gy (Figure 4). During the Re-irradiation, the child takes antiinflammatory therapy and tolerates well CSRT without side radiation toxicity.

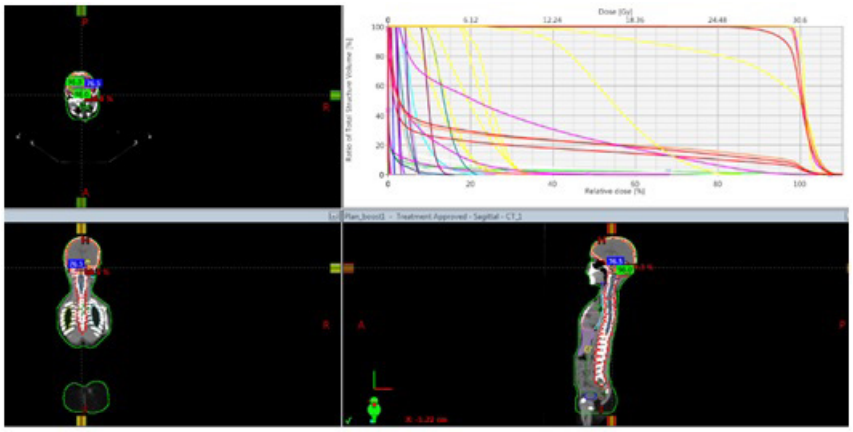

Figure 1: Intensity modulated cranio-spinal radiotherapy (CSRT) up to total dose (TD) 23.4 Gy with a boost in the tumor bed up to TD 54 Gy.

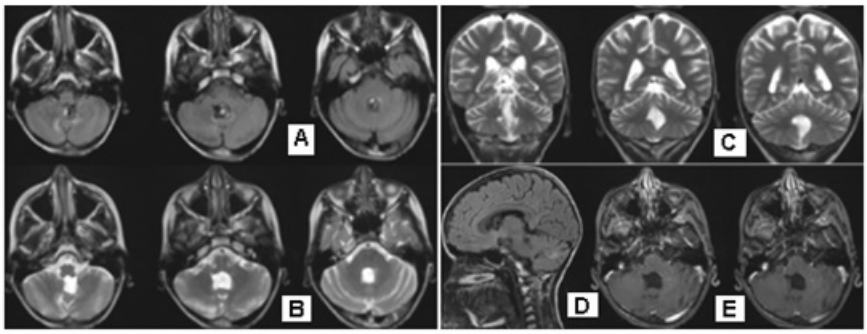

Figure 2: Brain MRT/ July 2019- A residual lesion measuring 4.5 mm without perifocal edema A/ Ax T2 FLAIR; B/ Ax T2 fr FSE; C/ COR T2 fr FSE; D/ Sag T2 FLAIR; E/Ax T1 FSPGR.

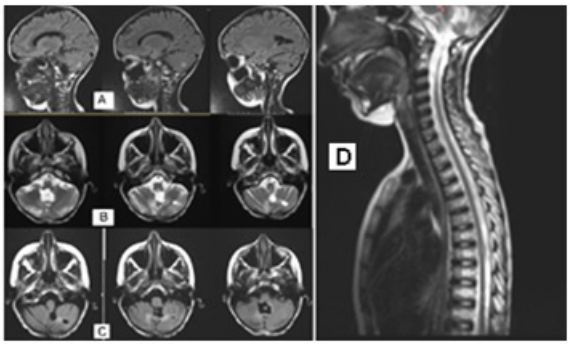

Figure 3: MRT/ March 2022- A second inoperable local recurrence without craniospinal leptomeningial metastases - A/Sag T2 FLAIR; B/ Ax T2 fr FSE; C/ Ax T2 FLAIR; D/ Sag T2 fr FSE.

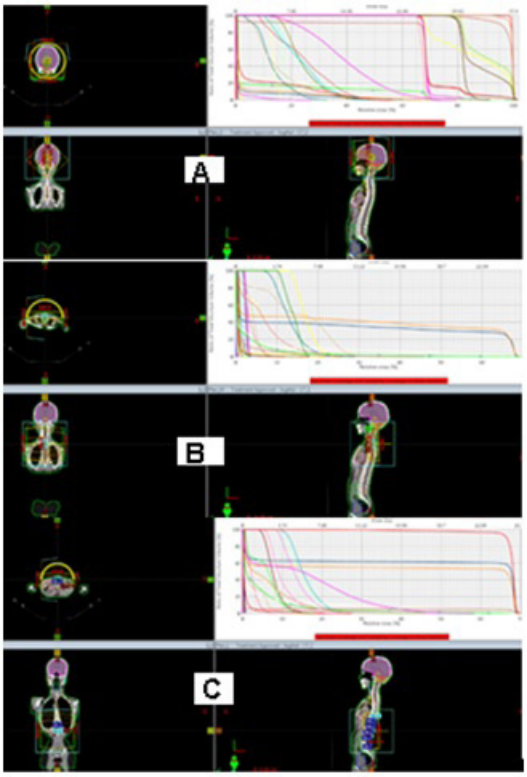

Figure 4: Intensity Modulated Cranio-spinal Re-irradiation with VMAT method with DD 1,5 Gy up to TD 23.4 Gy with a simultaneous boost in posterior cranial fossa with DD 1,8 Gy up to TD 30.5 Gy, as well as in the tumor bed with DD 2 Gy up to TD 34 Gy.

4. Discussion

Medulloblastoma (MB) is the most common malignant brain tumor of childhood, comprising about 20% of all pediatric brain tumors [12]. The traditional therapeutic mainstay for MB includes a multimodal approach with surgery, RT, and multiagent Ch [13]. At the time of diagnosis, gross total resection (GTR) of the primary tumor is standard of care. However, survival difference between GTR and near total resection (> 90% of tumor removed) has not been proven [14]. In a multicentric prospective single arm trial, 65 children (3–10 years of age) with nondisseminated MB were treated with postoperative, reduced-dose craniospinal RT (23.4 Gy) and 55.8 Gy of posterior fossa (PF) boost and the Ch regimen. Five-year progression free survival (PFS) was 79% [15]. Relapse treatment consisted of combinations of surgery (25%), focal radiotherapy (RT 22%), high dose Ch with stem cell rescue (HDSCR 21%) and conventional Ch (90%). In multivariate analysis; isolated relapse in PF, and surgery were significantly associated with prolonged survival whereas RT and HDSCR were not [16]. Patients who were not optimally staged at primary diagnosis (due to incomplete/poor quality MRIs or no central review of MRIs), or had excess residual tumour (>1.5 cm^2) on review, had a worse outcome [17,18]. However, a combined Children's Cancer Group-Pediatric Oncology Group study including 126 patients with low-stage MB comparing two different doses of neuroaxis irradiation (36 Gy in 20 fractions vs. 23.4 Gy in 13 fractions) led to early study termination after 16 months as a statistically significant increase was observed in the number of all relapses as well as isolated neuroaxis relapses in patients randomized to the lower dose of neuroaxis radiation [19,20]. Similar is the presented clinical case in which a low radiation dose was implemented in the cranio-spinal axis up to TD 23.4 Gy with a tumor bed boost up to TD 54 Gy (Figure 1). Due to complications of tachycardia, the first surgery remains with a volume of subtotal tumor resection, and subsequently no re-operation has been performed to precede the above described CSRT with a tumor bed boost. Clinical remission is achieved only after the completion of 8 courses of adjuvant Ch. The period of risk for recurrence of a congenital tumor is equal to the age at presentation of illness plus 9 months gestational time. The assumption is made that a tumor of embryonic origin will become manifest after a period of time determined by its inherent rate of growth and that tumor cells surviving treatment will multiply and present with recurrence in an equal period of time [21]. Consequently, the historic risk stratification system relying on the Chang staging system [22,23] with the risk factors residual disease >1.5cm^2, metastatic dissemination, and large-cell/anaplastic histology needed to be reconsidered. Most patients will relapse at distant CNS sites with or without disease in the original tumour bed. Individual reports indicate relapse can occur more than 5 years after diagnosis [2,3,16,24]. Survival after relapse was not related to biological factors and was very poor despite several patients receiving intensive treatments [25]. Several reports have demonstrated that the prognosis at relapse is poor, with generally less than 10% survival [25-27]. Older children (aged >3–5 years) with disease relapse who received conventional upfront therapy (neurosurgery, CSRT and Ch) are treated with various strategies at relapse, including metronomic therapy, high-dose Ch, intrathecal Ch, and re-irradiation [28-31]. In the clinical case presented due to an intraoperative complication, an interruption is required and it remains with a volume subtotal tumor resection with a residual tumor, well visualized on post-operative MRT (Figure 2). Treatment was continued with 8 courses adjuvant Ch, resulting in clinical remission. After 2 years, a first local recurrence was performed, which was radically operated, but treatment was continued with Ch and not with re-irradiation. Re-irradiation has been shown to be of benefit, and considering the high frequency of metastatic relapses in MB, craniospinal re-irradiation has been suggested as a therapeutic option worth exploring, although this requires careful balancing against the risk of side effects [30].Re-irradiation for recurrent pediatric MB can offer some patients disease control, particularly those with focally recurrent disease in the brain [32]. In select cases, re-irradiation for relapsed MB has achieved 5-year progression free and overall survival from first relapse of 48% and 65%, respectively [33]. The median interval between RT courses was 2.0 years (range 0.3-16.5). The median radiation dose and fractionation in equivalent 2-Gy fractions was 63.7 Gy (range

27.6-74.8) for initial RT and 53.1 Gy (range 18.6-70.1) for repeat RT [34]. Median interval from primary irradiation to re-RT was 49.5 months (range 24–98 months) with median cumulative biologically effective dose of 117 Gy (range 78–132 Gy) [35]. In a local recurrence, despite the visibly radical re-operation (Figure 3), craniospinal re-irradiation is required, which is possible after a 6-month interval from the previous CSRT (Figure 4). In progression of the disease, regardless of recurrence, local or metastatic in crani-spinal axis, the combination of the two local methods followed by Re-irradiation achieves improved PFS.

5. Conclusion

Medulloblastoma is the most common malignant brain tumour in children. The historic risk stratification system relying on the Chang staging system [22,23] with the risk factors residual disease >1.5cm2, metastatic dissemination, and large-cell/anaplastic histology needed to be reconsidered. Treatment is complex, including GTR, postoperative CSRT with high radiation dose in tumor bed and adjuvant chemotherapy. The optimal approach to treating relapsed MB in previously irradiated children remains in doubt. In cases where relapse is localised, surgical resection is appropriate. In a local recurrence, despite the visibly radical re-operation, craniospinal re-irradiation is required, which is possible after a 6-month interval from the previous CSRT with tumor boost. In progression of the disease, regardless of recurrence, local or metastatic in craniospinal axis, the combination of the two local methods followed by reirradiation achieves improved PFS.

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