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Re-Irradiation in the Treatment of Pediatric Central Nervous System Tumor Recurrence

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ABSTRACT

Aim: Radiotherapy is one of the main treatment modalities in childhood cancers,but it is a treatment method that is generally cautious due to its side effects.Central nervous system re-irradiation is the treatment choice that should be applied by considering the benefit-harm balance due to its side effects, especially radionecrosis.In this study, we aimed to report the results of the cases who underwent childhood CNS reirradiation,which is very disadvantageous in terms of toxicity.

Material and Methods: In this study,the data of patients with primary central nervous system neoplasm who received the repeat courses of RT in our department were retrospectively analyzed.Second-course RT is called reirradiation and is defined as prescribing radiotherapy to the field which overlaps with the first radiotherapy area.Data were obtained from patient files and planning system. Results: Six patients were included in this study.The primary diagnosis of 50% (n=3) of the patients is medulloblastoma.In the first treatment, craniospinal RT was applied to three patients. The median time between diagnosis and recurrence was 19.5(range 11-101) months.The median time between primary and secondary RT was 22(range 7-102) months.The BED3 equivalent of the dose received by the brain stem(BS) due to the first radiotherapy is a median 90(range 80.6-99.2) Gy.The primary RT BS EQD2 dose was median 52.2 (range 50-57)Gy. The median total dose of re-RT is 36 (range 20-50.4)Gy. The median BED3-BS for re-RT is 48.4 (range 11.5 -90) Gy. The median EQD2 brainstem for re-RT is 29 (range 7.2-54) Gy. During the follow-up period, 3 patients died. Three patients are alive at their 7, 12, and 27-month follow-ups and have no health problems related to the primary diagnosis.

Conclusion: Radio necrosis was not detected in any of the living cases in our study. Further studies are needed to select the appropriate patient and radiotherapy technique for reirradiation in pediatric CNS cases

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Introduction

CNS (Central nervous system) tumors constitute 20% of childhood tumors and are responsible for 30% of cancer-related deaths[1]. Frequently observed CNS tumors are, medulloblastoma, low and high-grade gliomas, and ependymomas. Combined modality therapy with chemotherapy, surgery, and radiotherapy is the standard treatment approach. However, recurrence can be observed in 30% of the patients usually with a dismal prognosis, and salvage treatment may be required. Management of these relapses is often challenging since there is little evidence to guide the decision-making process. Retrospective series have demonstrated long-term disease control e.g in ependymoma and medulloblastoma with second-course radiotherapy suggesting that Radiotherapy (RT) is a critical component of the multidisciplinary approach both in de-novo and recurrent tumor management. However, the developing pediatric brain is sensitive to radiation, and reirradiation (re-RT) must be weighed carefully against the acute and late effects[2,3].

In recent years, an increasing number of papers published regarding experience on re-RT of recurrent childhood tumors[4-9]. They are usually small case series and heterogeneous in almost all aspects including tumor type, surgical technique, chemotherapy regimen, and radiotherapy dose and fractionation. Since there is no possibility of a randomized trial with high-level evidence in the short term, so for now at least decisions must be guided on retrospectively reported clinical experience which makes this case reports valuable. Hence, we aimed to report the results of reirradiation for CNS recurrence applied to 6 pediatric patients treated at the Radiation Oncology Clinic of Ankara City Hospital within 2 years.

Materials and Methods

In this study, the data of patients with primary central nervous system neoplasm who received the repeat courses of RT in our department were retrospectively analyzed. Second-course RT is called reirradiation and is defined as prescribing radiotherapy to the field which overlaps with the first radiotherapy area. Patient examination information, patient files, RT plan details, and electronic system data were used for the study. Data regarding gender, primary histological type, age at the time of diagnosis and recurrence, the time between diagnosis and recurrence, age at the time of first-course RT and reirradiation, the time between two RT courses, location of primary disease, and recurrence data were obtained from patient files and planning system. The aim of the study was the time between primary and secondary RT and patients' compliance with treatment. Additionally, the localization and interval between RT were noted for a patient undergoing a different site RT.

Patients Selection

Pediatric patients who underwent re-RT for cranial spinal tumors in Ankara City Hospital between 14.03.2019 and 01.04.2022 were included in the study. Patients with missing data, out of follow-up, and patients over the age of 18 were excluded from the study.

Compliance with ethical standards

This study was carried out by the principles of the Declaration of Helsinki, considering these principles. Ethics committee approval was obtained for this study from Ankara Provincial Health Directorate, Ankara City Hospital, Clinical Research Ethics Committee No. 1 with the ethics committee number E1-21-1504 on 03/02/2021.

Results

Six patients who underwent CNS re-RT in Ankara City Hospital between 14.03.2019 and 01.04.2022 were evaluated retrospectively. The patients received multimodal treatment with surgery, chemotherapy, and radiotherapy according to their age and tumors first-line therapy. Patients who developed recurrences during their follow-up underwent resection if they were operable. Patients and treatment details are summarized in Table 1.

The primary diagnosis of 50 % (n=3) of the patients is medulloblastoma. In the first treatment, craniospinal RT was applied to three patients. Primary RT was administered to patients at a fraction dose of 1.8 or 2 Gy, with a median total of 54 (range 23.4-60) Gy. The BED3 equivalent of the dose received by the brain stem due to the first radiotherapy is a median 90 (range 80.6-99.2) Gy. The primary RT brainstem maximum EQD2 dose was calculated as a median 52.2 (range 50-57) Gy.

The median time between diagnosis and recurrence was 19.5 (range 11-101) months. The treatment of patients after recurrence is as follows; 3 patients (50%) CRT ; 2 patients (33.3%) surgery and RT; 1 patient (16.7%) Surgery + CRT. Local field Re-RT was applied to 3 different relapse sites of the patient who was diagnosed with high-grade glial tumors. Re-irradiations were planned using the IMRT and SRT techniques. The median time between primary and secondary RT was 22 (range 7-102) months. The median total dose of re-RT is 36 (range 20-50.4)Gy. The median BED3 for re-RT Brainstem is 48.4 (range 11.5 -90) Gy. The median EQD2 for the report brainstem is 29 (range 7.2-54) Gy.

During the follow-up period, 3 patients died. The causes of death of the patients were pneumonia, sepsis, and GIS bleeding. The remaining patients with two anaplastic ependymomas and one MB are alive. Three patients are alive at their 7, 1,2, and 27-month follow-ups and have no health problems related to the primary diagnosis.

Stable disease was reported in the follow-up imaging studies of these patients. Radionecrosis was not detected radiologically or clinically in any of the surviving patients. The third course of re-irradiation of the patient with a diagnosis of medulloblastoma under the age of 3 was interrupted at the request of the patient's family, and the patient died two months later. The technical characteristics of reirradiation are summarized in Table 2.

Discussion

In our study, the data of 6 patients who underwent cranial re-RT in our clinic were analyzed retrospectively. The median time between diagnosis and recurrence was 19.5 (range 11-101) months. The median time between primary and secondary RT was 22 (range 7-102) months. The patients were well tolerated and no serious treatment-related toxicity was observed. Radionecrosis was not detected radiologically or clinically in any of the surviving patients.

Wetmore and colleagues retrospectively reviewed 38 recurrent medulloblastoma patients of whom 14 of them received salvage RT and reported that the use of ReRT resulted in a statistically significant improvement in survival both for standard and high-risk patients compared to non-irradiated ones[7]. method, thereby obtaining information about the molecular subgroups of relapsed patients. They reported that patients who progressed > 4 months after the first course of RT and with focal brain recurrence experience longer survival. They also reported long-term survival for one patient with a wnt-activated subgroup and poor survival for one group 3 and 3 shh-activated subgroups after ReRT emphasizing the importance of molecular analysis in some aspects of salvage therapy decision. Emphasizing that molecular analysis may guide salvage therapy decisions.
In the study of Gültekin et al., in which they evaluated hypofractionated stereotactic radiotherapy (HFSRT) treatment in children, the results of 18 cases with primary CNS tumors were reported (8). Although a separate analysis was not performed in the primary brain tumors group, it was reported that the cumulative BED value, the time between two treatments, and the treatment technique did not affect local control. They observed 2 (9%) brain necrosis (grade 3 and grade 1) at 1 and 5 months post-ReRT and concluded HFSRT was safe.

In a multicenter study, Rao et al. presented the most extensive case series of 67 patients with recurrent CNS tumors[6]. Among these cases, one patient experienced seizures, somnolence, and edema post-ReRT (25 Gy total in 5 fractions) interpreted as radionecrosis, managed with high dose steroids but 2 months after treatment the patient also developed tumor progression, making the initial diagnosis suspicious.

We observed neither clinical nor radiological radionecrosis after conventionally fractionated ReRT with IMRT, although it is difficult to draw definitive conclusions with the short follow-up period and the small number of cases.

In all these studies, there is no optimal recommended RT technique or dose. As mentioned before, with the advances in radiotherapy, an increasing number of pediatric patients are treated with reirradiation salvage therapy. However, it is impossible to reach precise results due to the differences in radiotherapy dose, technique, recurrence pattern, presence of accompanying surgery, and systemic agents in current studies[10,11].

Proton therapy is another promising radiotherapy method in ReRT applications[12]. In the study reported by Farnia et al, re-irradiation results were reported in patients whose first treatment was also administered with proton therapy. No patient developed central nervous system necrosis requiring treatment. Although our center is new, 6 cases in 2 years show that these cases are increasing. Treatment decisions for these patients must be made in multidisciplinary meetings, and survival expectancy and toxicity possibilities must be considered. With improving techniques, radiotherapy has become increasingly involved in the treatment of CNS relapses, and the initial results are promising.

Limitations of the Study

The retrospective design of this study, the small number of cases, and the limited follow-up period do not make it possible to reach a general conclusion about the subject studied. However, since the subject has been reported with a limited number of cases in the literature, it was thought that this report would contribute to the literature.

Conclusion:

Following the rapid development of radiotherapy techniques, reirradiation therapies, which were not considered to be applied before, are increasingly used in childhood CNS relapses. More studies are needed for appropriate patient and treatment selection.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Table 1. Patient Characteristic

Table 2. Characteristics of patients' first radiotherapy and re-irradiation plans