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CLINICAL INVESTIGATION

PENTEC Organ-Specific Report: Brain and Brain Stem Necrosis After Reirradiation for Recurrent Childhood Primary Central Nervous System Tumors: A PENTEC Comprehensive Review

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Purpose

Reirradiation is increasingly used in children and adolescents/young adults (AYA) with recurrent primary central nervous system tumors. The Pediatric Normal Tissue Effects in the Clinic (PENTEC) reirradiation task force aimed to quantify risks of brain and brain stem necrosis after reirradiation.

Methods and Materials

A systematic literature search using the PubMed and Cochrane databases for peer-reviewed articles from 1975 to 2021 identified 92 studies on reirradiation for recurrent tumors in children/AYA. Seventeen studies representing 449 patients who reported brain and brain stem necrosis after reirradiation contained sufficient data for analysis. While all 17 studies described techniques and doses used for reirradiation, they lacked essential details on clinically significant dose-volume metrics necessary for dose-response modeling on late effects. We, therefore, estimated incidences of necrosis with an exact 95% CI and qualitatively described data. Results from multiple studies were pooled by taking the weighted average of the reported crude rates from individual studies.

Results

Treated cancers included ependymoma (n = 279 patients; 7 studies), medulloblastoma (n = 98 patients; 6 studies), any CNS tumors (n = 62 patients; 3 studies), and supratentorial high-grade gliomas (n = 10 patients; 1 study). The median interval between initial and reirradiation was 2.3 years (range, 1.2-4.75 years). The median cumulative prescription dose in equivalent dose in 2-Gy fractions ($EQD2_2$; assuming α/β value = 2 Gy) was 103.8 Gy (range, 55.8-141.3 Gy). Among 449 reirradiated children/AYA, 22 (4.9%; 95% CI, 3.1%-7.3%) developed brain necrosis and 14 (3.1%; 95% CI, 1.7%-5.2%) developed brain stem necrosis with a weighted median follow-up of 1.6 years (range, 0.5-7.4 years). The median cumulative prescription $EQD2_2$ was 111.4 Gy (range, 55.8-141.3 Gy) for development of any necrosis, 107.7 Gy (range, 55.8-141.3 Gy) for brain necrosis, and 112.1 Gy (range, 100.2-117 Gy) for brain stem necrosis. The median latent period between reirradiation and the development of necrosis was 5.7 months (range, 4.3-24 months). Though there were more events among children/AYA undergoing hypofractionated versus conventionally fractionated reirradiation, the differences were not statistically significant ($P = .46$).

Conclusions

Existing reports suggest that in children/AYA with recurrent brain tumors, reirradiation with a total $EQD2_2$ of about 112 Gy is associated with an approximate 5% to 7% incidence of brain/brain stem necrosis after a median follow-up of 1.6 years (with the initial course of radiation therapy being given with conventional prescription doses of ≤2 Gy per fraction and the second course with variable fractionations). We recommend a uniform approach for reporting dosimetric endpoints to derive robust predictive models of late toxicities following reirradiation.

Section snippets

Clinical Significance

Radiation therapy has an established role in the multimodality management of primary central nervous system (CNS) malignancies in children and adolescents/young adults (AYA).[1] Some children will develop local and/or regional intracranial recurrences following curative-intent radiation therapy. Reirradiation may be considered for recurrent or new primary CNS tumors.[2,3] A further course of radiation therapy may achieve long-term disease-free survival for some patients.4, 5, 6 However, determining …

Endpoints and Toxicity Scoring

The endpoints used for the comprehensive literature search included brain necrosis, neurocognitive impairment, and visual deficits following reirradiation for recurrent brain tumors. However, the literature review revealed sparse data for neurocognitive impairment and visual toxicities (Appendix E1). Therefore, this review focuses on necrosis in the brain and brain stem following reirradiation. Radiation necrosis is defined as cellular injury and inflammatory changes at the sites of radiation…

Anatomy and Developmental Dynamics

A separate PENTEC review on neurocognitive effects and necrosis gives a concise summary of brain development.[16] The brain stem, which connects the cerebrum to the spinal cord and cerebellum, starts developing during the fourth week of gestation, and the structural changes in gray and white matter compartments continue through childhood and adolescence.[36] The gray matter within the brain stem forms important brain stem nuclei and 10 cranial nerves (III-XII) emerging from the brain stem. The…

Defining Volumes: Pediatric Imaging Issues

The brain and brain stem can be delineated on the planning computed tomography (CT) scan, though coregistration of appropriate sequences of MRI scans with planning CT scans enables more accurate delineation of various anatomic substructures of the CNS such as the hippocampi. The brain volume includes the cerebellum, cerebral spinal fluid, and small brain vessels and excludes the brain stem and large cerebellar vessels such as the sigmoid, transverse, and superior sagittal sinuses.[40] The carotid …

Methodology

A comprehensive literature review was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[42] statement to identify all studies which evaluated the risk of brain/brain stem necrosis following repeated radiation therapy for pediatric brain tumors. The PubMed and Cochrane databases were searched for peer-reviewed articles in English published between January 1, 1975, and August 1, 2021. Investigators independently reviewed titles, abstracts, and…

Mathematical models

All studies broadly described techniques and range of doses used for reirradiation (Appendix E2). However, they lacked important details on clinically relevant dose-volume metrics (eg, volume of reirradiation treatment overlapping with primary radiation therapy volume, mean and maximum cumulative equivalent dose in 2-Gy fractions, with α/β value of 2 Gy [$EQD2_2$]) necessary for dose-response modeling on late CNS effects.[55,56] For this analysis, we calculated the cumulative $EQD2_2$ using median dose …

Toxicity Scoring Recommendations

Use of the CTCAE version 5.0 criteria for scoring toxicity for CNS necrosis (Table 2) is recommended.…

Data Reporting Standards Specific to the OARs in Brain Reirradiation

It is recommended that published data sets reporting on outcomes following reirradiation should include details that would enable data pooling and modeling and should include the following:

Patient-, disease- and treatment-related factors

- Sex and race…
- Age when treated with primary and repeat radiation therapy…
- Details of surgery during diagnosis and at relapse…
- Details of concomitant or adjuvant chemotherapy during primary and repeat radiation therapy…

Details of primary and repeat radiation therapy

- Time …

…

Future Investigations

Single-institutional studies on reirradiation are often small and have variations in patient selection, approach to reirradiation, and outcome reporting. Therefore, we recommend creation of an international database to prospectively collect data regarding children receiving reirradiation for primary CNS tumors (eg, treatments and outcomes) as a basis for improved bioeffect models of the risks of reirradiation related to variables such as cumulative radiation doses, volumes, and intervals…

Acknowledgments

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Disclosures: none.

Data Sharing Statement: Study data are stored in an institutional repository and are available upon request to the corresponding author.

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