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PENTEC ORGAN SYSTEM REVIEW

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.

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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.

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.[4-6] However, determining the reirradiation dose that optimally balances the potential benefits with the potential risks is challenging. This comprehensive Pediatric Normal Tissue Effects in the Clinic (PENTEC) review aims to describe the risk of brain and brain stem necrosis after reirradiation to the brain.[7,8]

Radiation therapy is an essential component of the primary management of most pediatric brain tumors.[1,9] Radiation therapy is given to the whole or partial brain based on the histologic subtype of the tumor.[10-12] In the United States, approximately 3300 new patients under the age of 16 years are diagnosed annually with primary CNS tumors, which comprise the most common solid tumors in children treated with radiation.[13] While radiation therapy results in excellent cure rates for CNS tumors, some children develop late neurologic adverse effects, and a proportion develop tumor recurrence that can both affect their quality of life and survival.[14,15]

In a selected group of children with brain tumors who develop recurrence, reirradiation is increasingly being used with encouraging outcomes.[3] However, there are no specific reirradiation guidelines in terms of patient selection, optimal techniques, or recommended doses. In a separate PENTEC report, Mahajan et al highlighted the risks of brain necrosis and neurocognitive effects in survivors of brain radiation therapy as children.[16] In that report, the risk of symptomatic brain necrosis was modeled using the Lyman-Kutcher-Burman model after calculating equivalent dose in 2-Gy fractions (EQD2) assuming α/β ratio of 3 Gy (a commonly used value for late-responding tissues). In the setting of no prior radiation therapy, the PENTEC model estimated a 5% risk of brain necrosis after 58.9 Gy at 2 Gy per fraction to any part of the brain, including the brain stem. The corresponding threshold cumulative dose for 5% risk of necrosis after reirradiation was 59.9 Gy, suggesting essentially zero recovery of tolerance between courses of radiation therapy. The modeling for necrosis in the Mahajan et al report, which primarily focused on the late effects following primary radiation therapy, incorporated only 2 studies of reirradiation.[17,18] Therefore, a further detailed analysis was carried out in this report to focus primarily on late effects following reirradiation.

Necrosis, one of the most feared consequences of radiation therapy to the brain, can be symptomatic or asymptomatic. Symptoms depend on location, extent, and severity of the necrosis and typically include focal neurologic deficits such as motor or sensory loss and cranial nerve palsies as well as more generalized symptoms of headache and seizure.[19]

Radiologically, necrosis typically manifests on magnetic resonance imaging (MRI) as increased heterogeneous contrast enhancement with edema within and around the irradiated volume and can often be difficult to differentiate from tumor progression.[20,21] Advanced MRI techniques such as diffusion-weighted imaging, susceptibility-weighted imaging, perfusion-weighted imaging (dynamic susceptibility contrast and pseudocontinuous arterial spin labeling), diffusor tensor imaging, and magnetic resonance spectroscopy may be helpful to differentiate necrosis from progression.[22,23] Positron emission tomography and single-photon emission computed tomography (SPECT), which provide functional information, are also being increasingly used in clinical practice.[24] A systematic review and meta-analysis suggested that SPECT and magnetic resonance spectroscopy are more useful than standard MRI in distinguishing necrosis from tumor recurrence.[25]

There is no consensus on radiologic criteria for brain or brain stem radiation necrosis, as distinction between

radiation therapy—induced white matter changes and radiation necrosis is difficult. Nevertheless, the definition of radiation necrosis in most studies included a new area of contrast enhancement and a new area of abnormal signal intensity or increased signal intensity on T2-weighted images within the radiation treatment volume.[26-29] A recent study has defined brain stem necrosis as new T2-weighted fluid-attenuated inversion recovery lesions with ring or irregular enhancement within the brain stem after radiotherapy.[30] Spontaneous resolution, substantial regression, and stabilization on serial imaging are also considered as criteria for brain/brain stem necrosis in some studies.[26,31] However, these criteria are more helpful to distinguish necrosis from tumor progression/recurrence when the imaging changes are asymptomatic.

Standard medical treatments for symptomatic necrosis are corticosteroids, bevacizumab, and hyperbaric oxygen.[19,32-34] In patients with medically refractory necrosis, surgical resection is a treatment option.[35] Surgical resection may also be considered to aid in diagnosing radionecrosis versus tumor progression.

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 therapy that manifest with clinical symptoms and/or typical imaging features. This analysis focuses on symptomatic or asymptomatic necrosis seen on imaging that necessitated a therapeutic intervention. Necrosis presenting as transient imaging changes without symptoms was not included for the analysis.

CNS necrosis was recognized as a distinct adverse event in the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 published in August 2006. The CTCAE version 5.0 defines CNS necrosis as "a disorder characterized by a necrotic process occurring in the brain and/or spinal cord." Most studies defined necrosis with imaging, clinical symptoms, and occasionally by histopathology without a uniform scoring system.

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 white matter tracts of the brain stem travel both to and from the brain. The brain stem has 3 sections, which, in the descending cranial-caudal order, are midbrain, pons, and medulla oblongata (often called medulla for short). All these sections develop from different primary and secondary vesicles of the embryo. The midbrain develops from the mesencephalon (both primary and secondary vesicles named the same), the pons from rhombencephalon, and metencephalon and the medulla from the rhombencephalon and myelencephalon. The midbrain connects the diencephalon superiorly, the pons inferiorly, and the cerebellum via the superior cerebellar peduncles posteriorly. The pons connects to the midbrain superiorly, the medulla inferiorly, and the cerebellum via the middle cerebellar peduncles posteriorly. The medulla connects to the pons superiorly, the spinal cord inferiorly, and the cerebellum via the inferior cerebellar peduncles posteriorly.

The cellular injury and inflammation from brain and brain stem necrosis can potentially cause permanent or temporary functional deficits. Necrosis may result from damage to the parenchymal microvasculature that causes hypoxic injury.[27,37,38] Symptomatic necrosis from direct brain injury or from the inflammatory cascade elicited during necrosis leads to edema and mass effect. Sometimes edema can occur without necrosis.[39] Symptoms are typically localized to the specific region involved and can manifest as seizures, motor/sensory deficits (supratentorial brain), cranial nerve palsies, or hydrocephalus (brain stem).

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 canal and cavernous sinuses should also be excluded from the brain volume. It can be difficult to identify different lobes and functional components of the brain using only the planning CT scan.

The brain stem extends from the superior border of the midbrain, which lies inferior to the third ventricle and the optic tracts, to the pyramidal decussation at the level of the foramen magnum, where the brain stem becomes the spinal cord. T1 (usually Magnetization-Prepared RApid Gradient Echo or equivalent) magnetic resonance images are particularly well suited for delineating the brain stem. The brain stem is delineated superiorly from the superior aspect of the nigral substance at the cerebral peduncle to the inferior limit of the medulla oblongata, which is at the superior tip of the

dens of second cervical vertebra.[40] The cerebral aqueduct is included in the brain stem volume until it transitions caudally into the fourth ventricle. The brain stem surface is defined as the outer 2-mm rind of volume, and the interior (core) is the part of the brain stem inside the 2-mm-thick surface. The brain stem volume increases linearly with age, and males have slightly larger brain stems than females.[41]

While all studies in this report provided comprehensive survival outcomes, few studies included details about dose and volume for the whole brain, partial brain, the brain stem, or other intracranial organs at risk (OAR).

Review of Dose-Volume Response Data and Risk Factors

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 the full text of any potential articles for eligibility. Information on study design, patient characteristics, treatment details, and outcome of interest were extracted using an electronic data form independently by 4 investigators (T.A., E.Y., D.S.T., M.T.M.). Studies with adequate qualitative or quantitative data on brain/brain stem necrosis for children treated with reirradiation were included in this report. However, some studies included both children and adults treated with reirradiation, and few studies reported outcomes separately for children and adults. Our report includes only those studies that reported a median age of <24 years at the time of reirradiation. Studies on repeat radiation therapy where second/subsequent treatment volumes did not overlap with previous volumes were excluded from this study. Specific information on treatment details and outcome for primary radiation therapy and reirradiation was recorded, including dose fractionation, the technique of radiation therapy, photon versus proton, interval between both courses of radiation therapy, and method of assessment of brain/brain stem necrosis (clinical vs imaging vs both). Most studies did not report details on salvage surgery and chemotherapy for recurrence.

A total of 1183 studies were identified at screening, and 92 studies included data on reirradiation for recurrent primary CNS tumors in children and AYA. After review by task force members, studies reporting on only adult patients, reirradiation for metastases, review articles, and studies with <5 patients were excluded (n = 55); data from the remaining 37 studies were captured for further screening. Seventeen studies (total of 449 patients) with relevant information on brain and brain stem necrosis were selected for analysis.[4-6,17,18,43-54] Figure 1 summarizes the selection and elimination process used to identify the eligible studies. Table 1 summarizes the details of selected studies, and Appendix E1 shows the details of the information captured on the data extraction form. In 15 studies, children were treated with primary and repeat photon radiotherapy.[5,6,17,18,43-46,48-54] In the study by Tsang et al, all patients (n = 101 patients) received primary photon radiation therapy, 13 received proton reirradiation, and the remaining received photon reirradiation.[4] In 1 study (n = 25), proton therapy was used for both the primary and second treatment.[47]

Review of Historical Dose-Volume Data

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 and median number of fractions of primary and reirradiation, assuming high dose-volume overlap of the 2 treatment courses and without applying any correction factor for tissue recovery between primary and second irradiation courses. When individual patient treatment and outcome data were available, we tabulated the data separately to calculate $EQD2_2$. Results from multiple studies were pooled by taking the weighted (based on sample size) average of the reported crude rates from individual studies.

Risk factors

The risk of necrosis following primary radiation therapy may depend on the age at treatment, the dose of radiation therapy, fractionation, irradiated volume, and the use of concurrent chemotherapy.[57,58] Other factors such as the time interval between the first and second courses of radiation, degree of overlap between the 2 courses, and other intervening interventions may also impact the risk of necrosis following reirradiation.[59] However, there are limited conclusive data quantifying the impact and interdependency of these factors on the risk of necrosis. Critical data for understanding these risks of necrosis would thus permit unraveling of the multiple variables as described previously. Due to the lack of reporting of this significant information in all the studies, the influence of these factors on the integrity of

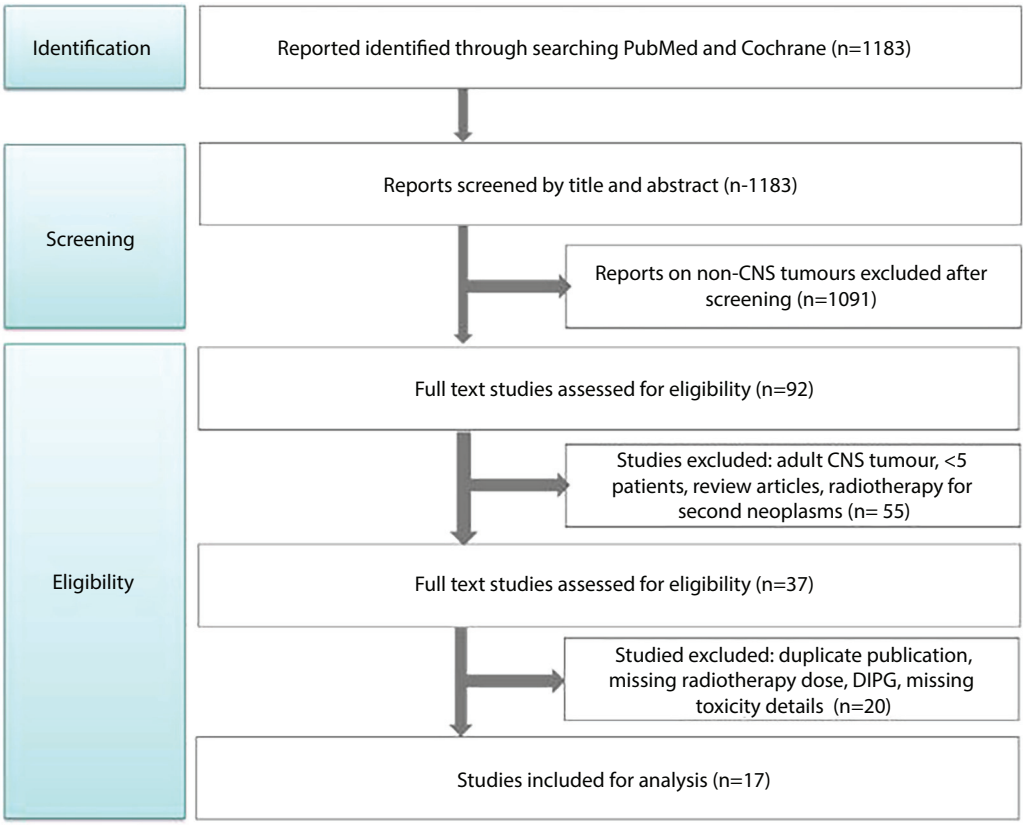

Fig. 1. Diagram showing identification, selection, and inclusion of published data. *Abbreviations:* CNS = central nervous system; DIPG = diffuse intrinsic pontine glioma.

irradiated tissues and the incidence of necrosis could not be evaluated.

While these factors could not be included in the PENTEC modeling for reirradiation, there are published data on the impact of some of these factors on risks of radiation-induced brain necrosis in the setting of no prior radiation therapy. In a study of 595 children treated with proton beam therapy, the risk of symptomatic brain stem injury was higher in those aged 3 years or younger (8.2% vs 1.9%; P = .005).[60] In another study of 313 children treated with proton therapy, children aged less than 5 years had a higher risk of brain stem toxicity than older patients (6.9% vs 1.1%; P = .01).[61] In a study of 171 patients, neither surgery before proton therapy nor number of surgeries were associated with an increased risk of radionecrosis.[29]

Although hydrocephalus before radiation therapy was associated with an increased risk of radionecrosis (hazard ratio, 2.41; 95% CI, 1.08-6.10; P = .035) in a recent study,[29] it was not a significant factor in another study.[60]

The histologic subtypes reported to be associated with a higher risk of radionecrosis include ependymoma versus nonependymoma (hazard ratio, 2.23; 95% CI, 1.07-4.72; P = .26)[29] and atypical teratoid rhabdoid tumor (ATRT) versus non-ATRT (11.6% vs 2.4%; P = .008).[60] The impact of histology may be confounded by factors such as the total radiation therapy dose and tumor location as well as age at the time of radiation therapy because these tumor types typically occur in younger children.

It is unclear whether radiation modality (photon vs proton) has an influence on the risk of radionecrosis. In a multi-institutional study of 107 children treated with photon therapy (median prescribed dose 55.8 Gy) for posterior fossa tumors without brain stem involvement, there were no grade ≥2 brain stem necrosis, and only 1.9% developed grade 1 necrosis.[30] A study of 216 children treated with proton therapy for medulloblastoma (n = 154), ependymoma (n = 56), and ATRT (n = 6) to a median dose of 54 Gy relative biological effectiveness (RBE) reported a 2% (95% CI, 0.7%-4.8%) 5-year cumulative incidence of brain stem injury.[62] Another study of 159 children with medulloblastoma treated with proton therapy reported a 10-year cumulative incidence of brain stem injury of 2.1%.[63] Another study of 468 children/AYA (medulloblastoma, 200; gliomas, 114; ependymoma, 87; and ATRT, 43) treated with proton therapy (median dose, 54 Gy RBE) reported asymptomatic brain stem imaging changes in 10.9% of patients.[60]

While there is no minimal recommended time interval between primary radiation therapy and reirradiation, the time interval is important in assessing feasibility and safety of reirradiation in terms of tissue recovery. The data on reirradiation in adults suggests that there is a meaningful degree of repair at ≥6 months.[64] There are prospective studies performed in primates demonstrating that the spinal cord

Table 1 Details of studies included in this analysis

First author	No. patients	Diagnosis	Initial RT dose (fraction size; Gy)	Median interval reirradiation (range; y)	Reirradiation dose (fraction size; Gy)	Cumulative RT dose, $EQD2_2$	No. brain necrosis (%)*	No. brain stem necrosis (%)*	Comments
Waxweiler[18]	23	DIPG	45-60 (1.8-2)	1.4 (0.3-11.7)	16-30 (6-8)	100.18	0	5 (22)	Initial median dose = 59.4 Gy, followed by median reirradiation dose of 25 Gy in 5 fractions. At median interval of 22 mo, 5 patients with brain stem necrosis.
Bauman[17]	30	All	50 (2)	1.4 (0.3-13.8)	20-110 (1.8-24)	79.7	3 (10)	0	Study involved 34 patients. In 30 patients, repeat irradiation overlapped with central nervous system volumes for cumulative doses of 56 Gy to 111 Gy (median, 79.7 Gy). (Overlap dose in 3 individual patients with necrosis: 0, 79.5, and 111 Gy.)
Tsang[44]	31	Ependymoma	54-59.4 (1.8)	1.9 (0.5-11.7)	15-59.4 (1.8-3)	107.7	0	0	Most patients received focal reirradiation.
Kano[46]	89	Ependymoma	54 Gy (1.8)	3.1 (0.2-17.8)	15 Gy (1.8-10)	115.05	7 (8)	0	Reirradiation median margin dose of 15 Gy (13 for grade 2 and 15 for grade 3 tumors). Seven patients had brain necrosis.
Tsang[4]	101	Ependymoma	37.8-69.6 (1.2-1.8)	2.2 (0.3-11.5)	36-59.4 (1.8)	107.7	7 (7)	3 (3)	Seven patients had brain necrosis and 3 had brain stem necrosis. Ten-year cumulative incidence of grade ≥3 necrosis was 7.9%. If including asymptomatic imaging changes, the cumulative incidence of any-grade necrosis was 26.9%.
Eaton[47]	14	Ependymoma	55.8 (1.8)	2.3 (1- 10.5)	14-55.8 (1.8-14)	55.8	0	1 (7)	Since the initial RT field included the upper cervical spine and brain stem, the additional dose to this area was limited to 16.2 Gy (and to a cumulative dose of 55.8 Gy). One patient had grade 1 necrosis.

(*Continued*)

Table 1 (*Continued*)

First author	No. patients	Diagnosis	Initial RT dose (fraction size; Gy)	Median interval reirradiation (range; y)	Reirradiation dose (fraction size; Gy)	Cumulative RT dose, $EQD2_2$	No. brain necrosis (%)*	No. brain stem necrosis (%)*	Comments
Hoffman[48]	11	Ependymoma	45-59.4 (1.8)	2.0 (not available)	24 (5-8)	116.43	0	5 (45)	Ten primary site recurrences and 1 local recurrence extending to the cervical cord. Primary RT: 55.8-59.4 Gy (1 patient received 45 Gy). Reirradiation: 10 patients 24 Gy in 3 and 1 patient 25 Gy in 5 (recurrence in the original field, which extended to the spinal cord); 5 patients with symptomatic brain stem necrosis. This series of reirradiation using fractionated SRS reported the highest risk of necrosis. However, it did not find any correlation between the risk of necrosis and the interval between radiation ($P = .56$).
Stauder[49]	19	Ependymoma	30-59.4 (1.8)	4.2 (0.5-14.3)	12-24 (1.8-14)	141.3	2 (10.5)	0	Two patients had brain necrosis; both had EBRT (no other details).
Bouffet[43]	14	Ependymoma	54-59.4 (1.8)	2.2 (1.1-9.4)	45-59.4 (1.8)	107.73	0	0	CTV/PTV margin is modified according to the proximity of the brain stem. One patient with radiation necrosis after radiosurgery; no details on dose.
Gupta[50]	28	Medulloblastoma	54.8 (1.8)	4.1 (2- 8.2)	30.6-50.4 (1.8)	117	0	1 (3.5)	Reirradiation to unifocal (18), multifocal (3), and CSI (7) region. One patient with repeated CSI developed necrosis.
Tsang[5]	14	Medulloblastoma	23.4-59.4 (1.8)	2.2 (1-8.5)	4-54 (1.8-10)	57.3-104.3	1 (7)	0	One patient had brain necrosis (in a supratentorial region that received 54 Gy + 30.6 Gy; EQD2, 80.4).
Wetmore[6]	11	Medulloblastoma	55.8 (1.8)	3.3(0.8- 8.9)	18-54 (1.8-18)	103.8	0	0	A total of 14 patients were in the study. After previous CSI, 8 patients had CSI reirradiation, and 3 had primary site reirradiation. Nine of 14 had grade 1-2 necrosis.
Bakst[53]	13	Medulloblastoma	54 (1.8-2)	4.8 (2.1-9.3)	19.8-45 (1.5)	85.8	1 (7.6)	0	Reirradiation for 6 infratentorial, 3 supratentorial, 1 CSI, and 1 whole brain region. The median cumulative dose was 85.8 Gy (range, 79.2-85.8) for supratentorial, 85.8 Gy (range, 84-98.4) for infratentorial, and 66 Gy for CSI region. One asymptomatic necrosis.

(*Continued*)

Table 1 (*Continued*)

First author	No. patients	Diagnosis	Initial RT dose (fraction size; Gy)	Median interval reirradiation (range; y)	Reirradiation dose (fraction size; Gy)	Cumulative RT dose, $EQD2_2$	No. brain necrosis (%)*	No. brain stem necrosis (%)*	Comments
Saran[51]	14	Medulloblastoma	50-55 (1.8)	4 (1-18)	30-40 (1.75-6)	140.55	1 (7)	0	Twelve patients with medulloblastoma and 2 patients with PNET. All had CSI initially. Reirradiation in 11 patients was with 30 Gy in 5 fractions, and in 1 was with 35 Gy in 5 fractions. Details of overlapping doses are not available. One patient had brain necrosis.
Milker-Zabel[52]	18	Medulloblastoma	54 (1.8)	2.8 (0.2-8)	15-24.5 (4-15)	79.7	0	0	Eighteen recurrences were in the boost volume (54 Gy) (total of 20 patients). Actively spared critical structures so that the percentage of the tumor volume below the 90% isodose in lesions treated with FSRT was 13% median (SD, 47.7%), and with SRS was 18.2% mean (range, 2%-38%). No necrosis was reported.
Chojnacka[54]	9	Medulloblastoma and germ cell tumors	40-55 (1.6-1.8)	3.3 (0.4-4.3)	28-40 (4-15)	72.18	0	0	Median cumulative BED was 144 (range, 126-181) (not clear if based on an α/β of 2 or 3). Recalculated EQD2, using data in their table, was a median of 72.18 (range, 60.23-90.56). No necrosis reported.
Tsang[45]	10	Supratentorial HGG	59.4 (1.8)	1.2 (0.8-4.6)	1.8-54 (1.8-3)	58.1-107.7	1 (10)	0	One patient had necrosis (grade 3).

Abbreviations: BED = biological effective dose; CSI = craniospinal irradiation; CTV = clinical target volume; EBRT = external beam radiation therapy; EQD2 = equivalent dose in 2-Gy fractions; $EQD2_2$ = cumulative prescription dose in equivalent dose in 2-Gy fractions, assuming α/β value = 2 Gy; FSRT = fractionated stereotactic radiation therapy; HGG = high-grade glioma; PNET = primitive neuroectodermal tumor; PTV = planning target volume; RT = radiation therapy; SRS = stereotactic radiosurgery.

* Rates shown are the reported crude incidence.

undergoes progressive degrees of recovery 12 to 36 months post fractionated radiation.[65]

Brain and brain stem necrosis

The incidence of necrosis, defined as imaging changes or clinical symptoms in the absence of radiologic tumor progression, was extracted for individual studies (Table 1). Treated cancers included ependymoma (n = 279 patients in 7 studies),[4,43,44,46-49] medulloblastoma (n = 98 patients in 6 studies),[5,6,50-53] any CNS tumors (n = 62 patients in 3 studies),[17,18,54] and supratentorial high-grade gliomas (n = 10 patients in 1 study).[45] The median number of patients in individual studies was 14 (range, 9-101); only 4 of the 17 studies included 30 or more patients.[4,17,44,46] The median interval between initial and reirradiation was 2.3 years (range, 1.2-4.75). The median cumulative $EQD2_2$ prescription dose was 103.8 Gy (range, 55.8-141.3). Figure 2 illustrates crude incidences of brain and brain stem necrosis versus cumulative EQD2 from published studies of toxicities after reirradiation in this analysis. EQD2 was calculated by summing prescribed doses from the first and second regimens converted into EQD2 using reported fraction size in each regimen with an assumed α/β ratio of 2 Gy (see Appendix E3 for a detailed discussion on α/β of the brain). The heterogeneity in data and reporting did not permit the use of any mathematical model for analyzing the risk of necrosis. Therefore, uncertainties of incidences were calculated as 95% CIs according to the β probability distribution using the betafit function in MATLAB (MathWorks). The article also provides a qualitative description of the data.

Among 449 children/AYA treated with reirradiation, 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. The median cumulative prescription $EQD2_2$ was 111.4 Gy (range, 55.8-141.3) among the patients with any necrosis, 107.7 Gy (range, 55.8-141.3) for brain necrosis, and 112.1 Gy (range, 100.2-117) for brain stem necrosis. In 6 studies (n = 176) of conventionally fractionated (≤2 Gy per fraction) reirradiation, 7 patients (3.9%) developed brain necrosis, and 4 (2.2%) developed brain stem necrosis. In the 5 studies (n = 160) of hypofractionated (4-24 Gy per fraction) reirradiation, 9 patients (5.6%) developed brain necrosis, and 10 (6.3%) developed brain stem necrosis. The rates of necrosis in the hypofractionated reirradiation group were not statistically different from the rate in the conventionally fractionated reirradiation group (Fisher exact test, 2-tailed; $P = .47$). The remaining 6 studies (n = 113) used a range of fraction sizes (1.8-24 Gy). However, 2 studies that used multifraction stereotactic radiosurgery (SRS) reported a higher of radiation necrosis.[18,48] In both these studies, the reirradiation volumes were either within or near the brain stem, suggesting that clinicians should be cautious in the use of multifraction SRS for reirradiation when the target volume is near critical organs. One study (n = 14) study reported cumulative dosing for individual OARs for 10 patients.[47] None of the other studies reported cumulative dosing for individual OARs. Some studies either limited the cumulative radiation dose to the critical OARs such as the brain stem and upper cervical cord[47,66] or used techniques to achieve steep dose fall-off to normal tissues with some compromise of target coverage.[52] Most studies did not report on planning priorities or details on optimization (Appendix E2).

There was no consistent approach to the time interval between primary radiation therapy and reirradiation. Among the studies included in this analysis, the shortest minimal interval between primary and reirradiation was 2.6 months,[46] and the minimal interval ranged from 2.6 months to 24 months (Table 1).

In the QUANTEC review, adults who received primary radiation therapy 72 Gy at 2 Gy per fraction were estimated to have an approximately 5% risk of brain necrosis at 5 years,[67,68] whereas there was <5% risks of severe or permanent neurologic toxicity with a dose of 54 Gy to the entire brain stem and 59 Gy to a volume of 1 to 10 cc when using conventional (≤2 Gy per fraction) in adults following primary radiotherapy.[67] In a separate PENTEC report, children receiving 72 Gy to the brain including reirradiation as a cumulative dose have 8.4% (95% CI, 5.5%-11.3%) risk of necrosis.[16] However, in that report, only 1 study of reirradiation was used for analysis.[17] This current report analyzed 17 studies and found that reirradiation with an $EQD2_2$ of about 112 Gy (with the initial course being given via conventional 1.8-2.0 Gy/fraction, and the reirradiation with variable fractionations) resulted in a weighted average of <5% to 7% incidence of brain/brain stem necrosis after a median follow-up of 2.3 years. The reported rates of necrosis from both QUANTEC and PENTEC were generated as simple weighted (based on sample size) averages of the reported crude rates from individual studies.

Dose-volume/outcome associations

Due to the paucity of dosimetric data for detailed analysis, we could not derive any dose-response for radiation-associated brain/brain stem necrosis.

Limitations of the study

The most significant limitation of the current report is that all the studies included in the models lacked details on dose and volume for the brain stem or brain. To best analyze the risks of complications resulting from reirradiation, cumulative dosimetry is needed. Ideally, initial and reirradiation image sets should be registered and doses summed to estimate cumulative doses in each individual patient. This was not done in any of the reviewed studies. Less accurate cumulative dose estimates might be made from the prescription doses if necrosis occurs in a region where none of the overlapping dose distributions has a steep gradient. Ten of the 17 reviewed studies provided patient-specific prescriptions with

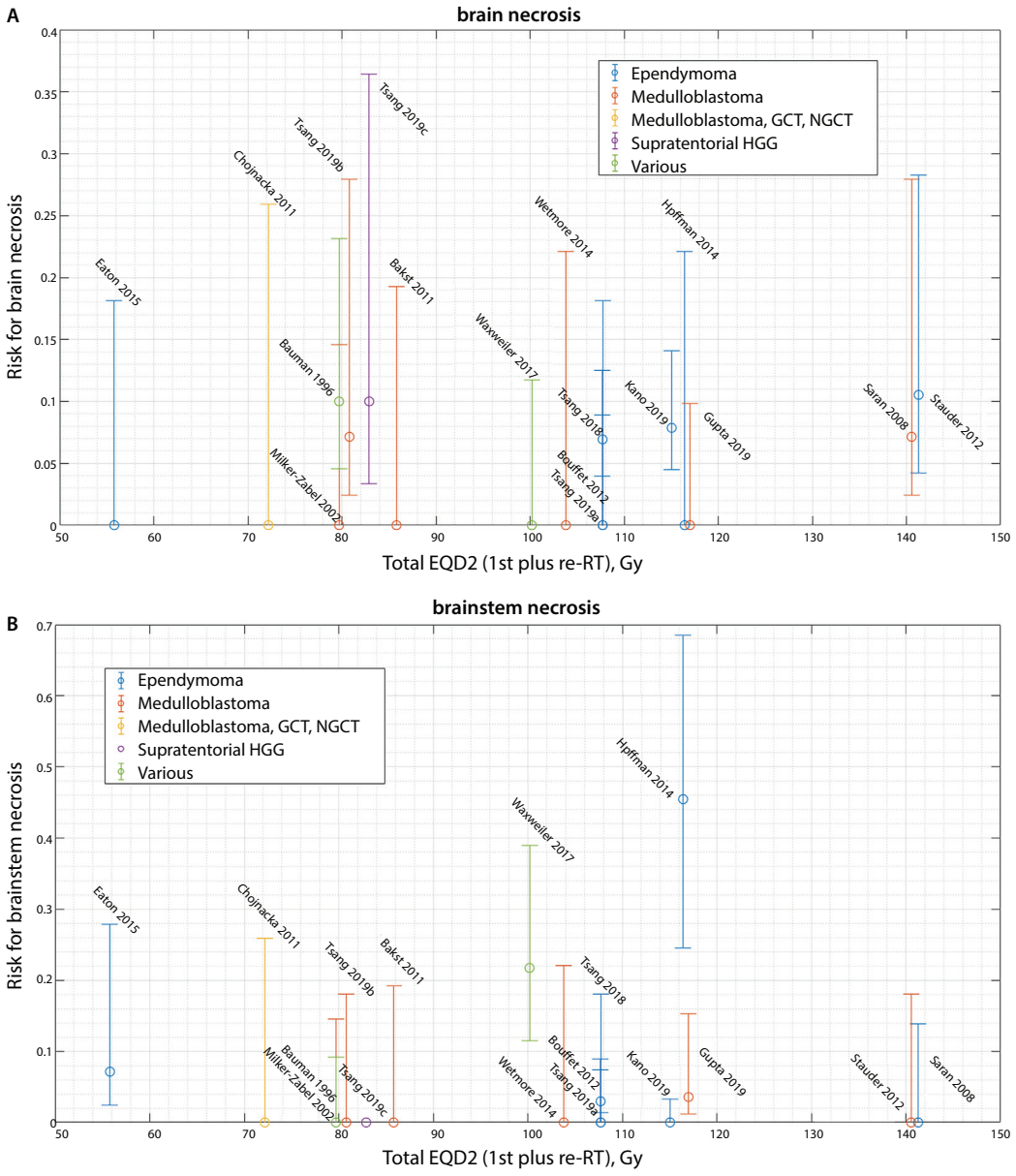

Fig. 2. Crude incidences of (A) brain and (B) brain stem necrosis versus cumulative equivalent dose in 2-Gy fractions (EQD2) from published studies of toxicities after re-treatments. EQD2 was calculated by summing prescribed doses from the first and second regimens converted into EQD2 using reported fraction size in each regimen with an assumed α/β ratio of 2 Gy. Doses were summed in the volumes overlapping from the 2 treatments when studies provided doses in the overlapping regions. Circles show the weighted (based on sample size) average of the reported crude rates for each individual study. The uncertainties of incidences were calculated as 95% CIs according to the β probability distribution using the betafit function in MATLAB (MathWorks). Text labels indicate first authors and year of publication, where Tsang 2019a, b, and c are references 45, 5, 46, respectively. *Abbreviations*: GCT = germ cell tumor; HGG = high-grade glioma; NGGCT = nongerminomatous GCT; RT = radiation therapy.

varying information about the degree of overlap; the others provided group statistics (ie, mean or median and ranges of prescriptions). The dosimetric quality of studies in Figure 2 is summarized in Appendix E4.[69] In the study by Tsang et al, all 101 patients received primary photon radiation therapy, 13 received proton reirradiation, and the remaining received photon reirradiation.[4] In 1 study (n = 25 patients), proton therapy was used for both primary and second treatment.[47] Both studies used Gy equivalents for proton treatment, and there were no data on RBE (beyond the standard 1.1 value) to do additional analysis. However, neither study reported any excess risk of necrosis with proton therapy.

The included studies were also heterogeneous in terms of histologic diagnoses, treatment techniques, and dose and fractionation for primary and reirradiation. In some studies, the treatment proactively avoided a high cumulative dose to

the brain stem and upper cervical cord by compromising the target volume coverage or reducing the total dose of reirradiation.[33,39] In other studies, it was not clear whether attempts were made to avoid high doses to the OARs. None of the studies reported the degree of overlap between primary and reirradiation volumes or dosimetric parameters (eg, maximum dose for serial organs, mean dose for parallel organs). In our analysis, we assumed overlap of a meaningful volume of the brain, though detailed data could not be extracted from the paper.

The reported risks of necrosis were estimates based on the average reported crude rates from individual studies considered; however, the data were not conducive to modeling. Given the lack of reported patient-level data on individual event times, we were unable to compute actuarial risks.

The interval between primary and reirradiation was variable, and there was no minimum interval for reirradiation. Only a few studies reported on salvage surgery and chemotherapy; both modalities could potentially modify the tolerance of brain tissues to reirradiation. Another limitation is the lack of consistency in defining necrosis. Some studies used clinical symptoms while others used imaging findings or a combination of clinical or imaging findings. Indeed, 1 study that explicitly included asymptomatic imaging-defined necrosis noted a very high rate of necrosis (27% in the study by Tsang et al).[4]

Important limitations are that there is no clear definition for reirradiation and no universally accepted consensus for clinical practice regarding reirradiation for pediatric brain tumors. Recently, the European Society of Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer developed a consensus statement on reirradiation based on an adapted Delphi process and systematic review of literature.[70] This consensus has proposed a clinically applicable definition of reirradiation, guidelines for reporting of clinical studies, and recommendations for decision making in clinical practice. This report defined reirradiation as a new course of radiation therapy either to previously irradiated volume, irrespective of concerns for toxicity (type 1 reirradiation), or to previously nonoverlapping irradiated volume where the cumulative dose raises concerns of toxicity (type 2 reirradiation). Irradiated volume is the volume of tissue receiving a clinically significant dose compared with normal tissue tolerance according to the International Commission on Radiation Units and Measurements report 50. Their recommendations regarding the reporting of clinical studies and decision making in clinical practice cannot be readily summarized, and the interested reader is encouraged to review the European Organisation for Research and Treatment of Cancer report.

The radiobiology of CNS necrosis is poorly understood. A definite value of α/β ratio for brain parenchyma is unknown, and it may range from 2 to 3. Most studies, especially those of hypofractionated radiation therapy, use a conservative value of 2 for dosimetric comparisons.[71,72] For example, in the HyTEC study, an α/β ratio of 2 was used to calculate single-fraction equivalent dose of multifraction SRS.[39] Using the linear quadratic model with an α/β ratio of 2 Gy, the authors modeled an approximately 3.4% risk of grade 3 toxicity for a V14 of 20 cm^3 that would be most applicable to multifraction regimens, approximately corresponding to a V23 in 3 fractions and V29 in 5 fractions. Thirteen out of 17 studies included in this analysis used a wide range of doses per fraction beyond the conventional fraction size of 2 Gy per fraction (Table 1). Therefore, this analysis is limited by the quality of the published data. To ensure consistency in comparing the range of dose fractionations used in different studies, after extensive discussion within the reirradiation working group, we have decided to use a conservative value of 2. The authors also felt that α/β ratio of 2 versus 3 is a minor point compared with the uncertainty in the literature from other factors (heterogeneous data sets, lack of patient-level data, etc). Appendix E3 discusses the α/β ratio for brain in detail. In real practice, until there is a global consensus to treat patients with reirradiation within a protocol, it is difficult to categorically say that whether an α/β ratio of 2 or 3 is most accurate. We think future reports of reirradiation could use both values of 2 and 3 to ensure possible radiobiological scenarios are covered.

Lack of consistency in imaging criteria for radiation necrosis is another limitation. While a new area of contrast enhancement and a new area of abnormal signal intensity or increased signal intensity on T2-weighted MRI within the radiation treatment volume[26-29] are essential criteria for radiation necrosis, a consensus on imaging criteria for brain and brain stem necrosis incorporating imaging changes during serial imaging and the evolving role of novel MRI techniques, positron emission tomography, and SPECT is urgently needed.

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

Table 2 Common Terminology Criteria for Adverse Events version 5.0 (2017)

Grade	Description
1	Asymptomatic, clinical or diagnostic observations only, intervention not indicated
2	Moderate symptoms, corticosteroids indicated
3	Severe symptoms, medical intervention indicated (eg, bevacizumab, hyperbaric oxygen)
4	Life-threatening consequences, urgent intervention indicated (eg, surgery)
5	Death

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 interval between individual courses of radiation therapy
- Sites of primary and repeat irradiation; state whether type 1 or type 2 reirradiation
- Prescribed radiation therapy dose, dose-fractionation, and EQD2 of individual courses of radiation therapy
- Details on any recovery factors have been applied for deciding reirradiation doses
- Radiation therapy techniques (ie, photon-based 2-dimensional, 3-dimensional, intensity modulated radiation therapy, volumetric modulated arc therapy; proton therapy including passive scatter, spot scanning, intensity modulated proton therapy, radiosurgery)
- Cumulative organ radiation exposure
  - Mean cumulative EQD2 dose using α/β ratios of both 2 and 3 for brain and CNS OARs
  - Maximum cumulative EQD2 dose (eg, D0.1cc) using α/β ratios of both 2 and 3

Details of assessment and follow-up

- Description of the toxicity endpoint including how it is measured and what toxicity scoring system was used (specifically clarifying symptomatic vs imaging-only endpoints)
- Frequency of clinical follow-up for late complications of radiation therapy
- Frequency of laboratory or imaging follow-up
- Number of patients in the study, number of those with or without toxicity; dosimetric data for both those with and without toxicity

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 between treatment courses (ie, understanding the pace and degree of normal tissue recovery between courses of radiation therapy). Such models will allow quantitative assessment of risk to inform decisions regarding reirradiation. Furthermore, there is an urgent need to have a consensus on radiological criteria for brain and brainstem necrosis.

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