NEUROSURGICAL FOCUS

Neurosurg Focus 53 (5):E2, 2022

Stereotactic radiosurgery for recurrent pediatric brain tumors: clinical outcomes and toxicity

***Elyn Wang, MD,[1] Paulina M. Gutkin, BS,[1] Justin Oh, MD,[1] Erqi Pollom, MD, MS,[1] Scott G. Soltys, MD,[1] Gerald A. Grant, MD,[2] Laura M. Prolo, MD, PhD,[2] Steven Chang, MD,[2] Gordon Li, MD,[2] Paul G. Fisher, MD,[3] Sonia Partap, MD,[3] Cynthia J. Campen, MD,[3] Iris C. Gibbs, MD,[1] and Susan M. Hiniker, MD[1]**

[1]Department of Radiation Oncology, Stanford University, Stanford; [2]Department of Neurosurgery, Stanford University, Stanford; and [3]Department of Neurology and Neurological Sciences, Stanford University, Stanford, California

OBJECTIVE Recurrence of brain tumors in children after the initial course of treatment remains a problem. This study evaluated the efficacy and safety of reirradiation using stereotactic radiosurgery (SRS) in patients with recurrent pediatric primary brain tumors.

METHODS This IRB-approved retrospective review included pediatric patients with recurrent primary brain tumors treated at Stanford University from 2000 to 2019 using frameless SRS. Time to local failure (LF) and distant intracranial failure (DIF) were measured from the date of SRS and analyzed using competing risk analysis. Overall survival (OS) and progression-free survival (PFS) were analyzed with the Kaplan-Meier method.

RESULTS In total, 37 patients aged 2–24 years (median age 11 years at recurrence) were treated for 48 intracranial tumors. Ependymoma (38%) and medulloblastoma (22%) were the most common tumor types. The median (range) single fraction equivalent dose of SRS was 16.4 (12–24) Gy. The median (range) follow-up time was 22.9 (1.5–190) months. The median OS of all patients was 36.8 months. Eight of 40 (20%) lesions with follow-up imaging locally recurred. The 2-year cumulative incidence of LF after reirradiation with SRS was 12.8% (95% CI 4.6%–25.4%). The 2-year cumulative incidence of DIF was 25.3% (95% CI 12.9%–39.8%). The median PFS was 18 months (95% CI 8.9–44). Five (10.4%) patients developed toxicities potentially attributed to SRS, including cognitive effects and necrosis.

CONCLUSIONS Reirradiation using SRS for recurrent pediatric brain tumors appears safe with good local control. Innovations that improve overall disease control should continue because survival outcomes after relapse remain poor.

https://thejns.org/doi/abs/10.3171/2022.8.FOCUS22361

KEYWORDS stereotactic radiosurgery; pediatric brain tumors; oncology

Approximately 27% of childhood malignancies are primary brain tumors.[1] The standard of care for most high-grade malignant brain tumors involves maximally safe resection (gross-total resection [GTR] or subtotal resection [STR]) and adjuvant chemoradiation.[2] Locally aggressive, recurrent nonmalignant primary brain tumors are also often treated with maximally safe resection followed by radiation. However, the recurrence of primary brain tumors after an initial treatment course that includes radiation therapy remains a challenge. Surgery and chemotherapy are frequently used as salvage options due to concerns about cumulative central nervous system (CNS) toxicity with reirradiation.

Several studies have shown the benefit of external beam reirradiation for recurrent CNS malignancies in adult patients.[3–5] However, the utility of conventional radiation techniques in reirradiation is limited by concern for high cumulative doses to normal tissue and increased risk of potential complications.[6] More precise radiation techniques, such as stereotactic radiosurgery (SRS), have provided another possibility for the use of reirradiation as a salvage option. SRS is a relatively new modality for the manage-

ABBREVIATIONS CNS = central nervous system; CSI = craniospinal irradiation; DIF = distant intracranial failure; DM = distant metastasis; GTR = gross-total resection; LF = local failure; LMD = leptomeningeal disease; OS = overall survival; PFS = progression-free survival; SFED = single fraction equivalent dose; SRS = stereotactic radiosurgery; STR = subtotal resection; WHO = World Health Organization.

SUBMITTED June 24, 2022. **ACCEPTED** August 9, 2022.

INCLUDE WHEN CITING DOI: 10.3171/2022.8.FOCUS22361.

* E.W. and P.M.G. contributed equally to this work. I.C.G. and S.M.H. share senior authorship of this work.

TABLE 1. Patient characteristics

Characteristic	Value
Patients	37
Age, yrs	
Initial diagnosis	6.68 (0.6–20.5)
Start of 1st SRS for recurrence	11.2 (2.7–24.8)
Sex	
Female	16 (43.2)
Male	21 (56.8)
Histologic type	
Ependymoma	14 (37.8)
Medulloblastoma	8 (21.6)
Embryonal tumor	5 (13.5)
Glioblastoma multiforme	3 (8.1)
Nongerminomatous germ cell tumor	2 (5.4)
Pilocytic astrocytoma	2 (5.4)
CNS embryonal tumor	1 (2.7)
Choroid plexus carcinoma	1 (2.7)
Meningioma	1 (2.7)
Grade at initial diagnosis	
I	2 (5.4)
II	7 (18.9)
III	5 (13.5)
IV	15 (40.5)
Not assessed	8 (21.6)

Values are shown as number, number (%), or median (range) unless indicated otherwise.

ment of pediatric brain tumors. SRS allows for precise delivery of high radiation doses with a steep dose drop-off to adjacent normal structures. This may optimize local tumor control while minimizing adverse radiation effects in the CNS such as cognitive decline[7] and myelopathy,[8] although radiation necrosis is a serious SRS dose-limiting complication that must be considered.[9] SRS has been used in many clinical settings with good success to treat adult tumor patients.[9,10] However, limited pediatric studies are available on SRS for the treatment of recurrent brain tumors in children. The aim of this study was to evaluate the efficacy and safety of SRS in pediatric patients with recurrent primary brain tumors.

Methods

In this retrospective analysis, pediatric patients treated with SRS for recurrent solid brain tumors at Stanford University from 2000 to 2019 were identified. We included patients as old as 24 years at the time of SRS who were treated with the initial course of tumor-directed therapy by pediatric neuro-oncologists at our institution. Patients with primary disease of the spine or extracranial sites were excluded. Patient demographic characteristics, tumor histology, and treatment details were recorded. Brain tumors diagnosed prior to 2016 were graded according to the 2000 World Health Organization (WHO) criteria, and the 2016 WHO criteria were used for tumors diagnosed thereafter.[11] This study was approved by the Stanford Institutional Review Board.

Radiation dose and fractionation were determined on the basis of previous exposure to radiation and tumor characteristics. Treatment planning did not include an additional margin around the tumor. SRS was delivered with the CyberKnife (Accuray) using previously described techniques.[12] All patients were treated in the outpatient setting and received 1–5 fractions on consecutive days. The single fraction equivalent dose (SFED) was calculated using established methods with alpha/beta equal to 10.[13]

Patients were evaluated with MRI every 3 months after SRS, as part of standard follow-up care. Dates of local and distant failure were collected. Tumor growth or recurrence after SRS was assessed by superimposing follow-up imaging onto the SRS treatment plans. The following parameters were evaluated: local failure (LF) within the SRS target volume, distant intracranial failure (DIF) outside the SRS target volume but within the cranium, and distant metastasis (DM) outside the cranium. Lesions were excluded if patients were lost to follow-up.

Adverse radiation effects were collected from clinic notes and imaging reports. These included radiation necrosis and symptomatic neurological dysfunction. Radiation necrosis was defined on the basis of radiographic evidence assessed using MRI with diffusion and/or perfusion imaging, or pathologic confirmation of necrosis was used in the absence of residual tumor in resected lesions. Necrosis was graded using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (US National Cancer Institute).

Statistical Analysis

Competing risk analysis was used to evaluate time from SRS treatment to LF, DIF, and DM with death as a competing risk. Patients without LF, DIF, DM, or death were censored at the date of last follow-up. Overall survival (OS) was calculated from the start date of the first SRS procedure to the date of death and censored at the time of the last follow-up. Progression-free survival (PFS) was calculated from the start date of the first SRS procedure to the date of LF, DIF, DM, or death. OS and PFS were analyzed using the Kaplan-Meier method. Data were analyzed per lesion (LF, DIF, and DM) and per patient (OS and PFS). Statistical analyses were performed with SAS version 9.4 (SAS Institute Inc.).

Results

Thirty-seven patients aged 2–24 years with recurrent primary brain malignancies were treated at Stanford University with image-guided SRS from 2000 through 2019. A total of 48 lesions were treated, and 40 lesions had evaluable follow-up imaging. The median (range) age at the start of SRS treatment was 11 (2.7–24.8) years.

Patient characteristics are summarized in Table 1. One patient (with pilocytic astrocytoma) was diagnosed with neurofibromatosis type 1. A second patient had a history of T-cell acute lymphoblastic leukemia 11 years before his embryonal tumor diagnosis; his leukemia had been treated

TABLE 2. Treatment history at first SRS treatment

Treatment	Value
Prior resections	1 (0–4)
Prior radiation treatments	1 (1–2)
Radiotherapy prescription	
Total dose, Gy	55.8 (39.4–60)
Dose/fraction, Gy	1.8 (1.67–8)
Total fractions	31 (3–33)
CSI	
Yes	19 (51.4)
No	18 (48.6)
Prior chemotherapy	
Yes	28 (76)
No	9 (24)

Values are shown as number (%) or median (range) unless indicated otherwise.

TABLE 3. SRS treatment details and toxicity

Characteristic	Value
SRS prescription, Gy/fraction*	
27/3	1 (2.1)
27.5/5	1 (2.1)
25/5	3 (6.3)
24/3	5 (10.4)
22/2	1 (2.1)
22/1	1 (2.1)
20/2	1 (2.1)
20/1	5 (10.4)
18/1	12 (25)
16/1	9 (18.8)
15/1	1 (2.1)
14/1	4 (8.3)
12/1	4 (8.3)
Tumor vol, cm^3	1.17 (0.02–42.5)
Site of SRS*	
Cerebrum	25 (52.1)
Frontal	13 (52)
Temporal	7 (28)
Occipital horn	1 (4)
Parietal	4 (16)
Posterior fossa	17 (35.4)
4th ventricle	3 (17.6)
Brainstem	10 (58.8)
Cerebellum	2 (11.8)
Internal auditory canal	2 (11.8)
Lateral ventricle	5 (10.4)
Pineal gland	1 (2.1)
Adverse radiation effects†	5 (13.5)
Symptomatic	3 (8.1)
Cognition	1 (33.3)
Necrosis	2 (66.7)
Asymptomatic	2 (5.4)
Necrosis	2 (100)

Values are shown as number (%) or median (range) unless indicated otherwise.
* Data are shown according to number of lesions (n = 48).
† Data are shown according to number of patients (n = 37).

with chemotherapy and a dose of 18 Gy for cranial irradiation. No other patients had known genetic syndromes or comorbid diseases.

Management of initial disease included surgery, radiation, and/or chemotherapy. Twenty-five (68%) patients initially underwent GTR, of whom 11 (44%) underwent reresection for tumor progression or recurrence. Three patients did not undergo resection as part of local management. All patients received radiotherapy to the brain prior to SRS treatment. Of these patients, 4 received 2 courses of radiotherapy to the brain prior to SRS. Chemotherapy was administered to 28 (76%) patients prior to SRS. Twenty-two (59%) patients received SRS at first tumor recurrence. Twelve (32%) underwent SRS for management of multiply recurrent disease. Treatment history is summarized in Table 2.

The median (range) SFED of SRS was 16.4 (2–24) Gy. The median (range) target volume for the recurrences was 1.17 (0.02–42.5) cm^3. Dose and fractionation regimens are described in Table 3. An average (range) 76% (64%–91%) prescription isodose line was used.

The median (range) clinical follow-up time was 22.9 (1.5–190) months. The median OS of all patients was 36.8 months (Fig. 1A). The median PFS was 18 months (95% CI 8.9–44.2). Of the 48 included lesions, 8 (3 patients) had no follow-up scans, were lost to follow-up, and were not included in the analysis of local or distant failures. Fourteen patients were treated with additional radiotherapy after subsequent progression. Among these, 1 patient underwent whole-brain radiation, 8 received 1 or more repeat SRS treatments, and 4 underwent both craniospinal irradiation (CSI) and SRS treatments. One patient developed progressive intracranial and spinal disease and underwent palliative resection of T2–3 intradural disease with decompression of the spinal cord, followed by postoperative radiation to the full spine and partial posterior fossa.

Local Failure

Of the 40 lesions that underwent follow-up imaging, 8 (20%) recurred locally at the site where SRS was administered (Table 4). These recurrences occurred in 8 different patients. The 2-year cumulative incidence of LF after reirradiation with SRS was 12.8% (95% CI 4.6%–25.4%) (Fig. 1B). Two of these patients received repeat SRS treatments. A summary of patient characteristics and treatment outcomes for local recurrence is depicted in Table 4.

Distant Failure

The 2-year cumulative incidence of DIF after reirradiation with SRS was 25.3% (95% CI 12.9%–39.8%) (Fig. 1C). In total, 14 patients had DIF. Two patients subsequently presented with leptomeningeal disease (LMD) after SRS. Three patients received CSI as subsequent treatments. One patient received whole-brain radiotherapy. Six

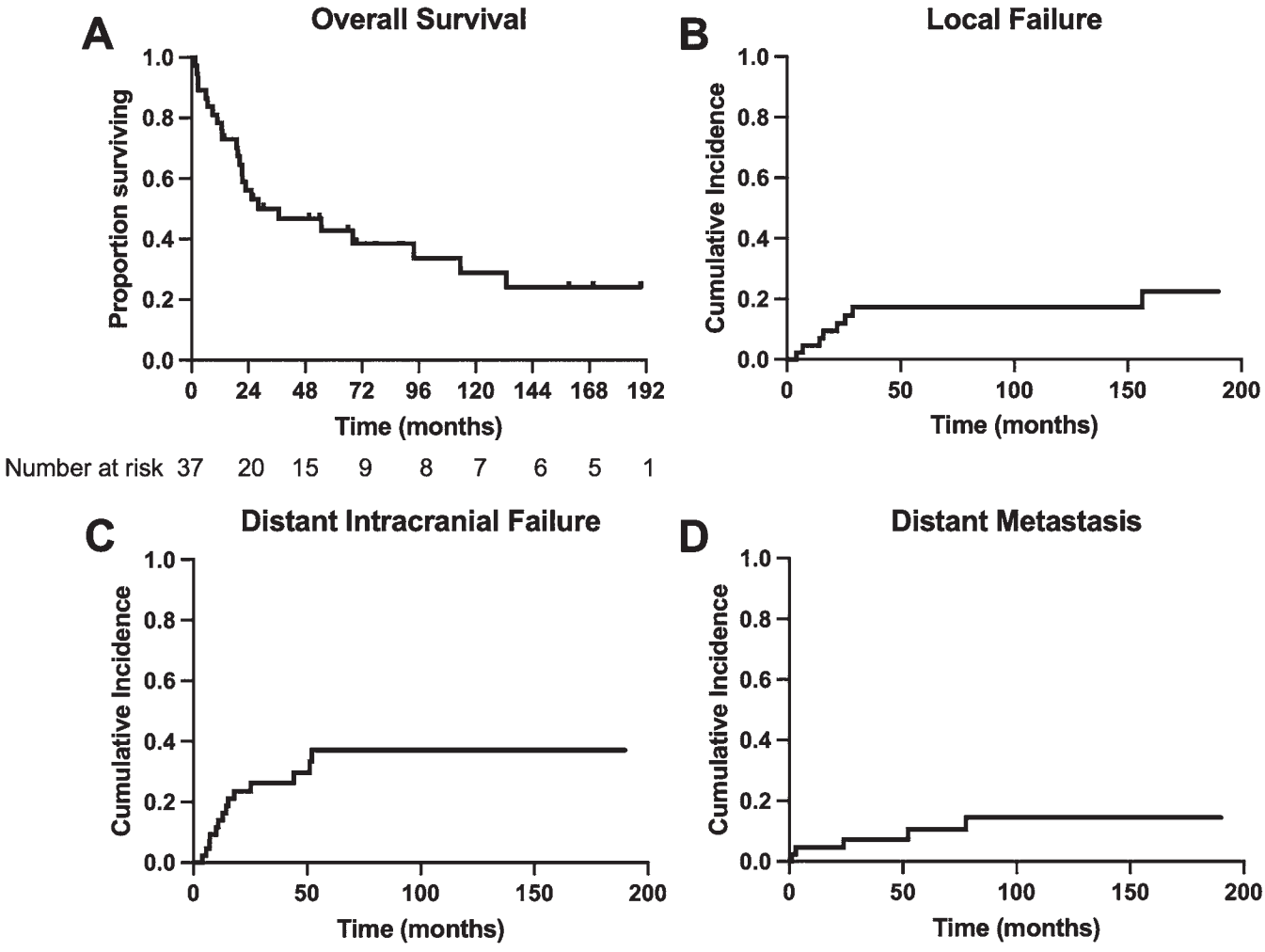

FIG. 1. OS and recurrence. **A:** Kaplan-Meier curve of OS (median survival 36.8 months) according to the proportion of surviving patients. The cumulative incidence curves for pediatric patients who received SRS are shown from the start of SRS to tumor growth or recurrence and according to the proportion of lesions. **B:** The 2-year cumulative incidence of LF after reirradiation with SRS was 12.8% (95% CI 4.6%–25.4%). **C:** The 2-year cumulative incidence of DIF was 25.3% (95% CI 12.9–39.8%). **D:** The 2-year cumulative incidence of DF after reirradiation with SRS was 7.9% (95% CI 2%–19.3%).

patients had 1–3 additional courses of SRS administered to new intracranial lesions after their initial SRS treatment.

Among the patients who developed LMD, 1 had an embryonal tumor in the right parieto-occipital region and initially underwent chemotherapy and radiation. She later had recurrence in the occipital region, for which she underwent SRS. She presented 10 months later with back pain, with MRI showing new LMD. She underwent surgery and a course of palliative radiation to the partial posterior fossa and whole spine. She continued to have disease progression throughout the brain and died. The other patient had a high-risk medulloblastoma treated with surgery, CSI, and chemotherapy. He first had recurrence 2 years later with an intramedullary lesion and was treated with surgery and SRS with chemotherapy. He had a second recurrence 6 months after SRS with enhancement along his posterior fossa resection cavity. He received SRS to this site, but follow-up MRI performed a month later showed multifocal relapse with LMD.

The 2-year cumulative incidence of DM after reirradiation with SRS was 7.9% (95% CI 2%–19.3%) (Fig. 1D). In total, 5 patients experienced DM. One patient (glioblastoma) developed malignant ascites diagnosed on the basis of peritoneal fluid found during ventriculoperitoneal shunt revision. He was in the process of receiving CSI due to high risk of LMD. Another patient developed recurrence in the proximal femur and neck (ependymoma) and subsequently received external beam radiotherapy at these sites. The third patient (embryonal tumor) developed recurrence in the abdomen and underwent exploratory laparotomy. A fourth patient (astrocytoma) developed metastasis to the thoracolumbar spine that was treated with GTR. He remains clinically stable with no evidence of new disease. The fifth patient (choroid plexus carcinoma) developed metastases to C5, T12, and L4, which were treated with CSI.

TABLE 4. Tumor and treatment characteristics of locally recurrent lesions (n = 8)

Patient No.	Sex	Age at Time of CK (yrs)	Genetic Syndrome	Tumor Histology	Grade	Site of SRS	SRS Dose (Gy)/ Fraction	Treatment Vol (cm^3)	Time From SRS to Local Recurrence (mos)	Additional Therapy	Outcome
4	Male	20.2	NF-1	Pilocytic astrocytoma	1	Superior vermis	22/2	0.58	22.06	Surgery	Deceased
7	Male	2.7	None	Ependymoma	3	4th ventricle	18/1	0.09	156.46	Surgery & SRS	Stable disease
11	Male	4.7	None	Ependymoma	3	4th ventricle	18/1	0.05	14.27	Surgery	Deceased
15	Female	5.1	None	Ependymoma	2	Prepontomedullary space	27.5/5	1.52	28.90	Neratinib	Deceased
17	Female	5.8	None	Embryonal tumor	4	Rt parietal occipital	24/3	14.34	25.58	Surgery & SRS	Deceased
23	Male	4.9	None	Ependymoma	3	Brainstem	25/5	1.80	6.97	Transferred to hospice	Deceased
29	Female	8.8	None	Ependymoma	Not assessed	Rt pontomedullary junction	24/3	4.19	15.95	Bevacizumab & erlotinib	Deceased
31	Female	24.8	None	Glioblastoma	4	Rt temporal	16/1	0.981	4.08	Surgery	Deceased

Adverse Radiation Effects

No patients experienced toxicity during the SRS treatment course. Late effects potentially attributable to radiation treatment included cognitive effects and radiation necrosis (Table 3). These were observed in 5 (13.5%) patients.

Cognitive Effects

One patient with a history of a multiply recurrent grade III fourth ventricle anaplastic ependymoma was initially treated with GTR alone in 2003. To date, she has had 5 recurrences of the tumor. On her first recurrence, she received local field radiotherapy (59.4 Gy) to the tumor bed. On the third recurrence, at the age of 4 years, she underwent her first SRS procedure to the resection cavity. She subsequently developed recurrence to the posterior fossa below the tentorium at age 8 years and to the third right dorsal medullary region at age 16 years. For each of these sites, she underwent either GTR or STR followed by SRS. She has since been managed conservatively. One month after her most recent SRS treatment, 16 years after her diagnosis, the patient reported difficulty with school, particularly with computation, processing speed, short-term memory, and visuospatial relationships. Although this was attributed to radiation exposure, multifactorial causes such as repeated surgical procedures and exposures to anesthesia were not ruled out. Currently, the patient benefits from an individualized learning plan at school. At the most recent follow-up 2 years after SRS treatment, she remains clinically stable without evidence of disease.

Radiation Necrosis

There were 4 occurrences of radiation necrosis, 2 of which were symptomatic (1 was grade 2 and 1 grade 4). The patient with grade 4 necrosis initially underwent STR of a grade III posterior fossa ependymoma followed by chemotherapy. He was treated with GTR followed by external beam radiotherapy at his first relapse. He developed progressive disease and received SRS to 3 lesions in the postoperative cavity (25 Gy in 5 fractions; equivalent dose in 2-Gy fractions [EQD_2] 31.3 Gy). Three months after SRS, imaging showed evidence of necrosis in the treatment volume, although the clinical status of the patient had improved. Seven months after SRS, the patient developed worsening drooling, immobile tongue, and hypertension. Imaging showed likely progressive tumor at the right medulla with admixed blood, although necrosis could not be excluded. Eight months after SRS, the patient developed worsening ataxia and right facial weakness, and imaging showed pathology that was interpreted as an admixture of progressive tumor, necrosis, and intratumoral hemorrhage with residual blood products. The patient died 3 months later.

The patient with grade 2 necrosis had a history of grade IV pineal nongerminomatous germ cell tumor with increased tumor marker levels and was treated with chemotherapy and craniospinal radiation. Six months later, he had recurrent eye paralysis and increased tumor marker levels, with his scan showing a large recurrent mass in the pineal region. He received chemotherapy followed by SRS to the tumor volume. Fourteen months after SRS, he experienced new-onset left-sided weakness and his MRI showed posttreatment changes secondary to radiation effects. He had normal tumor marker levels. He was started on dexamethasone with improvement of motor symptoms but with residual tremor.

One patient who was found to have asymptomatic radiation necrosis had a history of grade III supratentorial anaplastic ependymoma. He underwent multiple GTRs with 59.4-Gy doses for external beam radiotherapy at age 11 years. One year after administration of SRS (18 Gy in 1 fraction at age 13 years) to the left frontal bed, follow-up imaging showed increased size and intensity of enhancement at the posterior resection cavity within the SRS

treatment volume. This was worrisome for relapse versus treatment effect. He underwent resection after a PET scan showed uptake in the area of concern and pathological analysis demonstrated treatment effect without recurrence. Although no frank necrosis was identified, pathological analysis described the lesion as calcified with hyalinized blood vessels, which are features associated with radiation necrosis. At that time, he had stable right hand numbness with no new symptoms.

Finally, 1 patient was treated with SRS due to recurrent grade IV high-risk medulloblastoma at the posterior and left lateral aspect of the posterior fossa resection cavity. Over the course of several months, imaging showed stable size and the patient remained asymptomatic. T1-weighted gadolinium enhancement suggested radiation necrosis; however, this was not verified with pathological analysis. He later developed DIF throughout the left cerebellum, left middle cerebral peduncle, and left medulla and pons with facial and trigeminal nerve deficit. These tumors were deemed unamenable to a surgical approach; thus, no surgery or further SRS was recommended. He planned to start chemotherapy but ultimately died prior to initiation of treatment.

Discussion

Our study represents one of the few series on the use of SRS as a treatment for recurrent intracranial malignant pediatric brain tumors, with a median (range) clinical follow-up time of 22.9 (1.5–190) months. The median PFS was 18 months (95% CI 8.9–44.2). SRS may be a safe and viable treatment option for children with recurrent intracranial brain tumors who have previously been treated with different modalities.

Typical management of pediatric malignant CNS tumors often involves maximally safe resection with or without adjuvant radiotherapy/chemotherapy. However, recurrent brain tumors are particularly aggressive and recur both locally and distantly after initial treatment. Local control of these tumors is vital, and repeat surgical procedures carry a high risk of surgical complications. Reirradiation via external beam treatment to the CNS also carries significant risk of toxicities. Additionally, control outcomes are poor. Bauman et al.[14] reported a median PFS of only 3.3 months and median OS of 8.3 months, and Rao et al.[3] reported a median PFS of 7.9 months. As such, this study investigated the role of focal radiation therapy using SRS as a means of safely and effectively achieving local control in patients with these pediatric brain tumors.

The role of SRS in the treatment of recurrent pediatric brain tumors is still unclear, with limited data to guide management. The concern for potentially increased risks of late effects with the higher doses per fraction used in SRS, and the relative paucity of long-term data given the recent development of SRS techniques, has led to reluctance among some physicians to use SRS to treat pediatric patients. These potential risks are likely of even greater concern in the reirradiation setting. Merchant et al. reported a series of 6 pediatric patients who underwent a second course of radiotherapy for recurrent ependymoma.[15] Their patients were treated with a median dose of 18 Gy for SRS, with high rates of high-grade brainstem toxicity. However, other studies indicated that SRS for recurrent brain tumors may be safe and effective. Studies from Boston Children's Hospital[16] and University of Heidelberg[17] reported that SRS administered at median doses of 12 and 15 Gy, respectively, to children with recurrent medulloblastoma were not associated with any late toxicity after radiosurgery. Nanda et al.[18] also demonstrated that doses of 15–21 Gy for SRS were effective and well tolerated in 5 children treated for recurrent primary brain tumors, with 3 of 15 in-field failures and 1 case of asymptomatic radiation necrosis.

Our present findings suggest that SRS is a feasible option that provides good local control of recurrent intracranial tumors in pediatric patients, with a 2-year cumulative LF incidence of 12.8% and 1 case of grade 4 necrosis. Unfortunately, the DIF rate remained high at 25.3%. However, it is unlikely that treatment with wider fields such as with whole-brain radiation or CSI would result in improved outcomes because these modalities carry greater risks of cognitive and neurological effects than SRS without survival benefits.[19] Our study provides a basis for understanding the role of SRS in minimizing radiation toxicity and maximizing quality of life by delaying the need for more toxic options, such as whole-brain radiotherapy, or avoiding the need for additional salvage treatments. This approach to the treatment of recurrent brain tumors may allow for greater quality of life with minimal treatment sessions for patients with limited life expectancy, while providing similar local control.

This study was limited by its small sample size, single-institution experience, and retrospective nature. It is worth noting that most patients in this study had ependymoma, a disease that typically carries a better prognosis than medulloblastoma, after recurrence. Additionally, although we identified low rates of adverse events, the adverse effects of SRS should not be underestimated and may include cognitive decline, tissue necrosis, motor impairment, brainstem toxicity, and cerebrovascular impairment.[20] Causes of pathologic symptoms are often multifactorial, and the late effects of SRS may occur months to years after single-fraction administration. Due to the retrospective nature of the present study, it was unclear whether the adverse events could be attributed specifically to radiation, particularly because multiple modalities were used to treat patients. Thus, our study may have overestimated the rate of radiation toxicities.

Overall, the prognosis of recurrent intracranial brain tumors remains poor, and effective therapy that improves both local and distant control is needed. Our study demonstrated that SRS may be safe for recurrent pediatric brain tumors with good local control rates, with recognition that these patients require close follow-up due to the high risk of late distant recurrence. Patterns of recurrence (distant vs local) and molecular diagnostics[3] will be increasingly important in the future to guide appropriate treatment selection for these aggressive tumors. Additional prospective studies with longer follow-up duration and larger sample size are warranted for this group of patients with poor prognosis in order to gain a better understanding of the roles of various salvage treatment techniques and their long-term effectiveness and toxicity.

Conclusions

Our institutional experience with SRS for reirradiation of recurrent pediatric brain tumors adds to the literature supporting that this appears to be a safe technique in carefully selected patients, with good local control outcomes. Distant failure remains a problem, and further study is needed to improve overall patient outcomes after relapse.

References

1. American Cancer Society. Cancer Facts & Figures 2021. Accessed September 1, 2022. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2021/cancer-facts-and-figures-2021.pdf
2. Albright AL, Pollack IF, Adelson PD. *Principles and Practice of Pediatric Neurosurgery*. 3rd ed. Thieme Varlagsgruppe; 2015.
3. Rao AD, Rashid AS, Chen Q, et al. Reirradiation for recurrent pediatric central nervous system malignancies: a multi-institutional review. *Int J Radiat Oncol Biol Phys*. 2017;99(3):634-641.
4. Tsang DS, Sarhan N, Ramaswamy V, et al. Re-irradiation for children with recurrent medulloblastoma in Toronto, Canada: a 20-year experience. *J Neurooncol*. 2019;145(1):107-114.
5. Veninga T, Langendijk HA, Slotman BJ, et al. Reirradiation of primary brain tumours: survival, clinical response and prognostic factors. *Radiother Oncol*. 2001;59(2):127-137.
6. Taunk NK, Moraes FY, Escorcia FE, Mendez LC, Beal K, Marta GN. External beam re-irradiation, combination chemoradiotherapy, and particle therapy for the treatment of recurrent glioblastoma. *Expert Rev Anticancer Ther*. 2016;16(3):347-358.
7. Brown PD, Ballman KV, Cerhan JH, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): a multicentre, randomized, controlled, phase 3 trial. *Lancet Oncol*. 2017;18(8):1049-1060.
8. Hall WA, Stapleford LJ, Hadjipanayis CG, Curran WJ, Crocker I, Shu HKG. Stereotactic body radiosurgery for spinal metastatic disease: an evidence-based review. *Int J Surg Oncol*. 2011;2011:979214.
9. Kowalchuk RO, Niranjan A, Lee CC, et al. Reirradiation with stereotactic radiosurgery after local or marginal recurrence of brain metastases from previous radiosurgery. *Int J Radiat Oncol Biol Phys*. 2022;112(3):726-734.
10. Maranzano E, Terenzi S, Anselmo P, et al. A prospective phase II trial on reirradiation of brain metastases with radiosurgery. *Clin Transl Radiat Oncol*. 2019;17:1-6.
11. Kleihues P, Sobin LH. World Health Organization classification of tumors. *Cancer*. 2000;88(12):2887.
12. Gibbs IC. Frameless image-guided intracranial and extracranial radiosurgery using the Cyberknife robotic system. *Cancer Radiother*. 2006;10(5):283-287.
13. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol*. 1989;62(740):679-694.
14. Bauman GS, Sneed PK, Wara WM, et al. Reirradiation of primary CNS tumors. *Int J Radiat Oncol Biol Phys*. 1996;36(2):433-441.
15. Merchant TE, Boop FA, Kun LE, Sanford RA. A retrospective study of surgery and reirradiation for recurrent ependymoma. *Int J Radiat Oncol Biol Phys*. 2008;71(1):87-97.
16. Patrice SJ, Tarbell NJ, Goumnerova LC, Shrieve DC, Black PM, Loeffler JS. Results of radiosurgery in the management of recurrent and residual medulloblastoma. *Pediatr Neurosurg*. 1995;22(4):197-203.
17. Milker-Zabel S, Zabel A, Thilmann C, et al. Results of three-dimensional stereotactically-guided radiotherapy in recurrent medulloblastoma. *J Neurooncol*. 2002;60(3):227-233.
18. Nanda R, Dhabbaan A, Janss A, Shu HK, Esiashvili N. The feasibility of frameless stereotactic radiosurgery in the management of pediatric central nervous system tumors. *J Neurooncol*. 2014;117(2):329-335.
19. Brown PD, Ahluwalia MS, Khan OH, Asher AL, Wefel JS, Gondi V. Whole-brain radiotherapy for brain metastases: evolution or revolution? *J Clin Oncol*. 2018;36(5):483-491.
20. Rahman R, Alexander BM, Wen PY. Neurologic Complications of cranial radiation therapy and strategies to prevent or reduce radiation toxicity. *Curr Neurol Neurosci Rep*. 2020;20(8):34.

Disclosures

Dr. Soltys is a consultant for Accuray and receives non–study-related clinical or research support from Novocure. Dr. Gibbs receives honoraria from Accuray.

Author Contributions

Conception and design: Hiniker, Wang, Gutkin, Oh, Grant, Fisher, Gibbs. Acquisition of data: Hiniker, Wang, Gutkin, Oh, Fisher, Partap, Campen, Gibbs. Analysis and interpretation of data: Hiniker, Wang, Gutkin, Oh, Prolo, Fisher, Gibbs. Drafting the article: Hiniker, Wang, Gutkin, Oh, Pollom, Prolo, Chang, Li, Partap, Gibbs. Critically revising the article: Hiniker, Oh, Pollom, Soltys, Grant, Prolo, Chang, Li, Fisher, Partap, Campen, Gibbs. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Hiniker. Statistical analysis: Wang, Gibbs. Administrative/technical/material support: Gibbs. Study supervision: Hiniker, Gibbs.

Correspondence

Susan M. Hiniker: Stanford University, CA. shiniker@stanford.edu.