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Salvage Radiosurgery for Recurrent Supratentorial Primitive Neuroectodermal Tumors: A Single Institutional Series and Review of the Literature

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Abstract
Introduction: Supratentorial primitive neuroectodermal tumor is a rare, aggressive intrinsic brain tumor with limited treatment options for recurrent disease. SRS as a treatment modality in the recurrent setting was investigated. ***Methods:*** A retrospective review of 8 patients treated with SRS for local or distant recurrence of supratentorial PNET from 1999 to 2014 was conducted. ***Results:*** Thirty-six tumors were treated in 15 sessions in 8 patients. The median patient age was 22.5 (interquartile range [IQR], 14.75–43.5 years) with a median 21-month period from diagnosis until SRS (IQR, 16–23.75 months). The median prescription isodose volume was 1.85 cm^3 (IQR, 1.85–7.02 cm^3); median tumor margin dose was 18 Gy (IQR 14–20 Gy); and median isocenters was 2 (range 1–13). No patients experienced adverse radiation effects. All but 1 patient died, and the median overall survival was 32 months (IQR, 26.75–53.5 months) with median overall survival following SRS of 9.5 months (IQR, 5.25–30 months). Univariate analysis failed to demonstrate a statistically significant association between age, number of gamma knife treatments, interval to gamma knife, and margin radiation dose with overall survival. ***Discussion/Conclusion:*** This series supports the use of SRS in patients with recurrent supratentorial PNET following multimodal therapy.

Introduction

Supratentorial primitive neuroectodermal tumors (SPNETs) resemble medulloblastomas on histology and, thus, historically were grouped in a similar category of tumor [1]. This classification has undergone refinement in the era of genetic characterization of brain tumors. Genetically, SPNETs were felt to represent a distinct entity, characterized with more frequent copy number aberrations than medulloblastomas, predicting a more malignant course [2, 3]. Loss of 14q, 19q, and CDKN2A/CDKN2B as well as gain of 19p is observed exclusively in SPNET compared to gain of 17q in medulloblastomas [4–6]. Prognostic markers for SPNET including elevation of LIN28 and OLIG2 correlated with a shorter overall survival [7]. However, more recent molecular analysis re-

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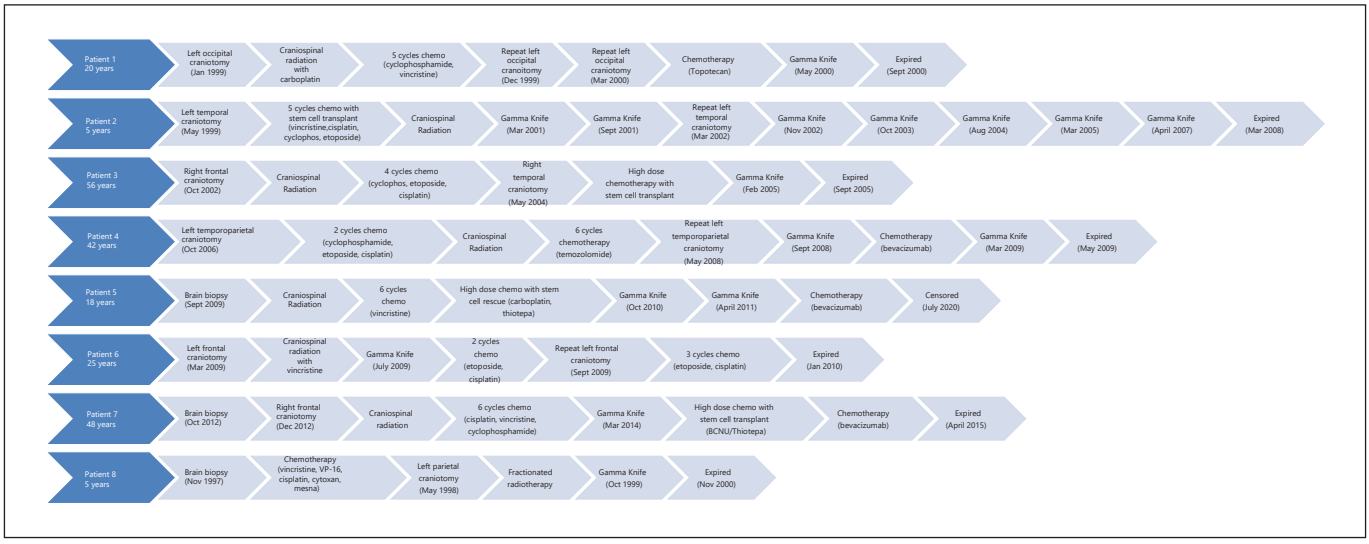

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Fig. 1. Clinical summary of each patient including age at diagnosis and chronological treatment approach.

vealed SPNETs represent a heterogeneous group of tumors, and the diagnosis of SPNET was removed from the WHO 2016 classification of central nervous system (CNS) tumors to be replaced by CNS embryonal tumor and further subcategorized based on presence of C19MC amplification on chromosome 19 [8]. Given our cohort is from prior to the 2016 reclassification, we present them as their original histology was diagnosed.

Treatments at initial diagnosis in major series consist of maximal safe resection, chemotherapy, and radiotherapy. Chemoradiation often includes craniospinal irradiation with concurrent weekly chemotherapy (e.g., vincristine) followed by 8 cycles of adjuvant chemotherapy often including a combination of vincristine and 1-(20chloroethyl)-3-cyclohexyl-nitrosourea (CCNU) [9]. In craniospinal irradiation, the primary tumor site (tumor plus 2 cm margins) is often treated to 54 and 36 Gy is delivered to the craniospinal axis with dose reductions for age <3 years. Myeloablative chemotherapy is often employed as a salvage treatment in the case of relapsed disease or upfront in high-risk cases at some centers (residual tumor >1.5 cm^2 after surgery or leptomeningeal seeding at diagnosis) [10, 11]. For this approach, following the collection and cryopreservation of hematopoietic stem cells multiple conditioning regimens have been reported with combinations of thiotepa, etoposide, cyclophosphamide, melphalan, and carboplatin [12, 13].

SPNET treatment at recurrence is not well defined. The safety and efficacy of SRS following craniospinal radiation originated in the pediatric literature for children with recurrent or residual medulloblastomas [14], and a similar study was extended into a limited adult population [15]. Herein, a primarily adult cohort population undergoing single-fraction salvage radiosurgery for recurrent disease is presented as a potential treatment option in this difficult clinical situation.

Materials and Methods

Patients

A retrospective review of 8 patients treated with at least 1 gamma knife procedure for a recurrent supratentorial PNET from 1999 to 2014 was conducted with appropriate approval from the Mayo Clinic Institutional Review Board (IRB # 20-008527). Patients (or their parents or guardians) provided their written informed consent. All patients had a histologically proven diagnosis of SPNET. Patients with an infratentorial PNET or PNET of the pineal region were excluded due to different genetics and prognosis underlying these lesions. All patients underwent initial multimodal treatment with a combination of surgery/biopsy, chemotherapy, and radiation therapy (shown in Fig. 1).

Patient 2 underwent 2 gamma knife procedures for a left sylvian fissure lesion (3/1/01) and cerebellar lesion (9/1/01) at an outside institution prior to treatment at our facility. Three patients underwent further salvage treatment with bevacizumab. Table 1 summarizes the patient characteristics.

Radiosurgery Technique

The Leksell Gamma Knife system Model B (for patients treated in 1999 and 2000), Model C (for patients treated 2002–2007), and PERFEXION (for patients treated 2008–2014) (Elekta Instruments, Norcross, GA, USA) system was used to deliver stereotactic radiosurgery treatments. All tumors were treated with single-frac-

Table 1. Summary of patient characteristics

Patient characteristics	
Age, yr, median (IQR)	20 (14.75–43.5)
Male, *n* (%)	5 (62.5)
Primary tumor site	
Temporal	3
Frontal	3
Thalamic	1
Parietal	1
Prior craniotomy, *n* (%)	8 (100)
Prior radiation therapy, *n* (%)	8 (100)
Prior chemotherapy, *n* (%)	8 (100)
Median time to SRS, m, median (IQR)	21 (16–23.75)
Post-SRS median overall survival, m, median (IQR)	9.5 (5.25–30)
Median overall survival, m, median (IQR)	32 (26.75–53.5)

IQR, interquartile range.

tion radiosurgery, but 1 patient had their treatment delivered over 2 days during a single episode of care. Dose planning using Leksell GammaPlan software was based on a stereotactic MRI. Dose selection was based on volume and proximity to vital structures, and also accounting for prior radiation by a team of radiation oncologists, neurosurgeons, and medical physicists. Table 2 outlines the dosimetric details for the study.

Follow-Up and Statistical Analysis

MRI at 3-month intervals during the first year was performed on all patients as feasible after SRS (2 patients did not have follow-up scans). Median and interquartile ranges (IQRs) were used to evaluate patient, tumor, and SRS variables. The primary endpoint of the study was overall survival. The Kaplan-Meier method was used to calculate the survival curve as a function of time. Cox regression modeling was used for univariable analysis. Statistical analysis was performed using RStudio software Version 1.3.1093.

Results

Patient Characteristics

Eight patients underwent a total of 15 SRS procedures to treat a total of 36 tumors. The majority of tumors were either frontal or temporal in location. The median patient age at presentation was 22.5 (IQR, 14.75–43.5 years). There were 2 pediatric patients and 3 patients over the age of forty.

Clinical Characteristics

There was a median 21-month period from diagnosis until SRS (IQR, 16–23.75 months). Median follow-up was 9.5 months (IQR 6.75–22.25 months). The median number of treatment sessions per patient was one, and the highest number of treatment sessions for a single patient was 7 over a period of 6 years.

Radiosurgery Parameters

The median prescription isodose volume was 1.85 cm^3 (IQR, 1.85–7.02 cm^3). The median tumor margin dose was 18 Gy (IQR 14–20 Gy), and the median maximal dose was 35.5 Gy (IQR 28–40). The median number of isocenters was 2 with a range of 1–13.

Clinical Outcomes

No patients experienced adverse radiation effects. Out of the 36 tumors, 31 had another MRI for follow-up after gamma knife treatment. Three tumors failed locally after gamma knife but also had evidence of distant recurrence on the same follow-up scan. Six patients failed at a distant site, 4 of whom with imaging consistent with leptomeningeal failure. Two patients were without imaging in our system during at least 4 months prior to expiration and the failure pattern was undetermined. Three patients went on to receive bevacizumab as a salvage treatment. All but 1 patient died (all due to their CNS disease and not unrelated causes), and the median overall survival was 32 months (IQR, 26.75–53.5 months) with median overall survival following SRS was 9.5 months (IQR, 5.25–30 months).

Univariate analysis examining age (hazard ratio [HR] 1.024, 95% confidence interval [CI] 0.98–1.069, $p = 0.3$), number of gamma knife treatments (HR 0.724, 95% CI 0.42–1.23, $p = 0.2$), interval to gamma knife (HR 0.86, 95% CI 0.73–1.02, $p = 0.07$), and margin dose (HR 0.991, 95% CI 0.73–1.35, $p = 1$) demonstrated no association with overall survival.

Discussion

To our knowledge, this is the first reported series describing outcomes of a predominantly adult population treated with SRS for recurrent SPNET. SRS can be an important salvage strategy in the setting of recurrent disease following multimodal initial therapy. In general, we observed 2 different treatment responses. The first category of patients included those who continued to progress rapidly after SRS. This group included 4 patients with survivals after SRS of 3 months ($n = 1$), 6 months ($n = 1$), and 7 months ($n = 2$). The second category had sustained clinical responses following SRS though these patients often

Table 2. SRS dosimetry parameters

	Date SRS	Target matrix	Isocenters, *n*	Volume treated, mm^3	Margin dose, Gy	Maximum dose, Gy	Local control
Patient 1	19 May 2000	Left occipitoparietal	8	3,540	14	35	*
Patient 2	14 Oct 2003	Left middle fossa	4	320	15	30	Yes
		Left lateral ventricle	2	130	15	30	Yes
	22 Nov 2002	Right optic tract	8	320	14	35	Yes
	31 Aug 2004	Left temporal	2	120	14	28	Yes
	15 Mar 2005	Left frontal	4	230	14	28	Yes
		Left basal ganglia	2	220	14	28	Yes
	13 Apr 2007	Left cerebellum	2	110	14	27.9	*
		Left middle fossa	6	1,160	14	27.5	*
		Left ventricle	5	190	14	28	*
Patient 3	11 Feb 2005	Right temporal	4	1,000	15	30	Yes
Patient 4	29 Jan 2009	Right sylvian fissure	6	640	10	25	Yes
		Right splenium	2	180	10	25	Yes
		Right temporal	4	650	10	25	Yes
	25 Sep 2008	Right temporo-occipital	13	2,990	10	25	Yes
Patient 5	15 Oct 2010	Left occipital	1	566	18	22.5	Yes
		Left cerebellum	1	414	18	22	Yes
	6 Apr 2011	Left cerebellum	1	94	22	44	Yes
		Left anterior temporal	1	93	22	44	Yes
		Right temporal	**1**	94	22	44	Yes
		Left posterior temporal	4	644	20	40	Yes
		Left medial trigone	2	232	20	40	Yes
		Right thalamus	2	502	20	40	Yes
		Left lateral trigone	4	863	20	40	Yes
		Right medial trigone	1	295	20	40	Yes
	7 Apr 2011	Right inferior corona radiata	1	93	21.3	42.6	No
		Right superior corona radiata	4	286	19.4	38.8	No
		Right superior frontal gyrus	1	93	21.6	43.2	Yes
		Left corpus callosum	3	603	19.2	38.4	Yes
		Left corona radiata	3	117	18.7	37.4	Yes
		Left anterior frontal	1	93	21.8	43.6	Yes
		Right lateral temporal	1	93.6	21.2	42.4	Yes
Patient 6	7 Jul 2009	Right frontal	2	100	20	40	No
Patient 7	26 Mar 2014	Right inferior frontal	6	714	18	36	Yes
		Right superior frontal	2	315	20	40	Yes
Patient 8	19 Oct 1999	Left frontal	7	690	15	30	*

* Patient did not have a follow-up MRI after SRS.

required repeat SRS for recurrence of disease (shown in Fig. 2). This group included 4 patients who survived at least 1 year after SRS with 2 patients surviving >7 years after SRS. There are <10 cases of reported long-term adult survivors with SPNET in the literature, and our cohort adds to the treatment strategies resulting in long-term survivors [16–18].

In terms of known overall prognosis for SPNET in adults, in a review of 103 adults 2-year overall survival rates are 35% and decline to 16.5% at 5-years [19]. Sur-

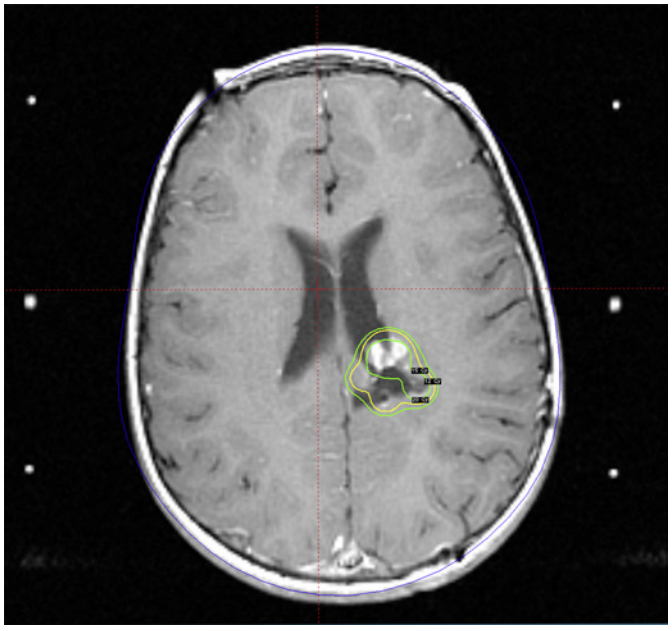

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Fig. 2. MRI of a representative treatment plan in a pediatric patient who had a recurrence at the anterior margin of the prior resection cavity. The 20, 15, and 12 Gy isodose lines are denoted.

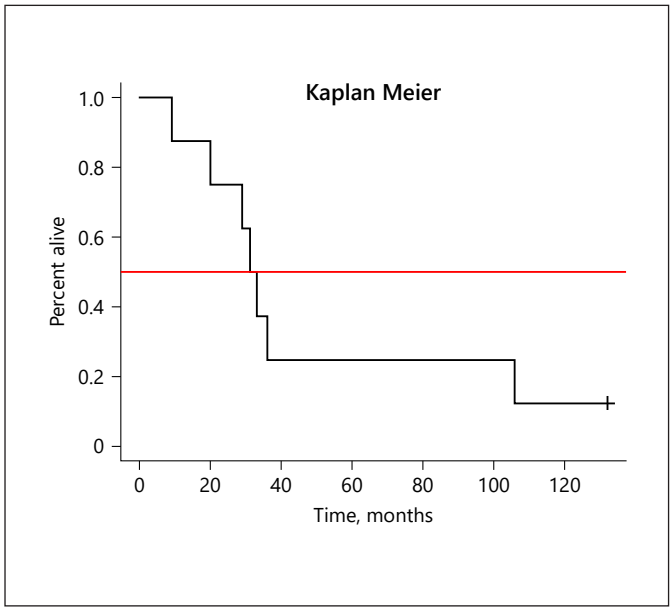

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Fig. 3. Kaplan-Meier plot of all 8 patients in the cohort demonstrating the survival rates of SPNET with a median overall survival of 32 months indicated by the intersection of the curve with the red 50% line.

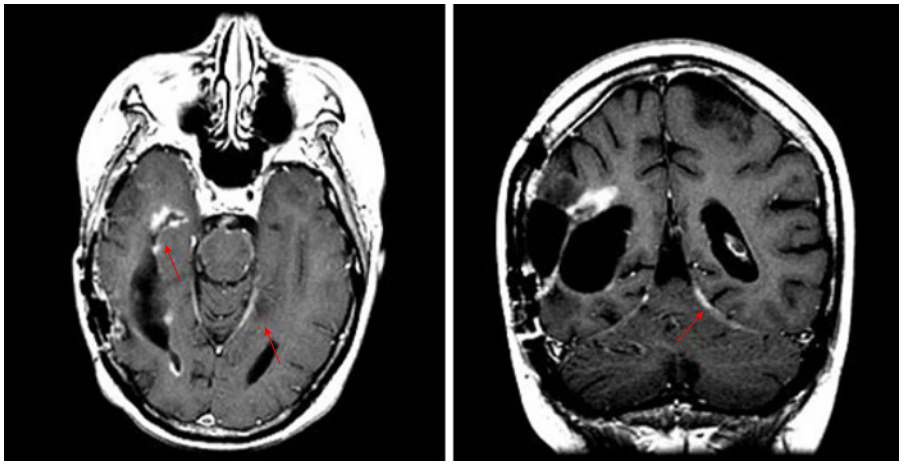

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Fig. 4. Axial and coronal contrast-enhanced MRI of leptomeningeal disease progression characterized by ependymal enhancement along the right temporal horn (arrow) and dural enhancement of the left tentorium (arrow) in a 42-year-old female with headaches and vomiting who underwent 2 prior gamma knife treatment sessions. Leptomeningeal dissemination was the most common pattern of treatment failure.

vival in pediatric populations is slightly better with 34% at 3-years and 18% at 5-years [20]. In our series, median overall survival was superior with a median overall survival of 32 months and 2 patients with greater than 5-year survival (shown in Fig. 3). Local control after SRS was achieved in 28 of 31 tumors with posttreatment imaging available. Distant recurrence was the dominant failure pattern in the majority of patients (6 patients), often with leptomeningeal dissemination (shown in Fig. 4). This is despite all but 1 patient receiving prior craniospinal irradiation. This is in agreement with previously published findings describing adults more frequently experience recurrence distant from the index tumor site [21].

Within the existing literature, there are only 2 other cohort studies with a homogenous population recurrent PNETs treated with SRS (Table 3). The first was published in 2009 and describes 7 pediatric patients with PNETs, and however, 5 of the patients had tumor location in the posterior fossa and 1 was pineal, which is both known to carry an improved prognosis and distinct ge-

Table 3. Literature review of retrospective studies on gamma knife for SPNET

Author (citation)	Patients, *n*	Patients with supratentorial disease, n	Median patient age, years	Median interval from diagnosis to SRS, months	SRS treatments, *n*	Median prescription isodose volume, cm^3	Median marginal dose, Gy	Median overall survival, months	Median post-gamma knife survival, months
Flannery et al. [22]	7	2	4.9	25.8	15	3.9	14.5	37	15.0
Se et al. [16]	11	11	17.0	72.5	11	17.5	11.5	65	17.0
Renfrow et al. (current study)	8	8	22.5	21.0	16	1.85	18.0	32	9.5

netics [22]. The second cohort study was published in 2016 and describes 11 patients, half of them adult, with all tumors supratentorial in location [16]. This series had an extended interval from diagnosis to SRS (median 72.5 months), contributing to a prolonged median overall survival of 65 months and median survival after SRS of 17 months. Compared to the study of Se et al. [16], our series had an older median age (22.5 vs. 17 years), which is has been shown to negatively impact prognosis [19]. Also, the impact of dose and local control remains unclear. No correlation between dose and local control was noted by Se et al. [16] (median margin dose, 11.5 Gy) or in our cases (median margin dose, 18 Gy). Further, dose evaluation was limited by the number of patients in this study and represents an area for further work in the future.

Our study is limited by the small sample size given the rarity of the disease and retrospective design which limits our ability to draw any definitive conclusions. Future, studies will benefit from molecular classification of this historic and heterogeneous diagnosis. Pooled analyses of rare tumor entities are warranted to better inform selection of patients who may benefit from local modalities including SRS at recurrence as compared to patients who are most likely to have diffuse progression and need systemic therapies.

Conclusion

Patients with SPNETs can be safely treated with SRS at recurrence after multiple types of prior therapy. SRS provided local tumor control without radiation-related complications in the majority of patients who had recurrent disease after resection, fractionated radiation therapy, and chemotherapy. The dominant failure pattern, despite prior craniospinal irradiation, emphasizes the need for new strategies to address leptomeningeal disease spread as it continues to drive mortality.

Statement of Ethics

Our manuscript is reported within Mayo Clinic institutional guidelines with the written consent of the patients (or guardians) and with IRB approval (protocol number 20-008527).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Jaclyn Renfrow, MD – data acquisition, analysis, interpretation, literature review, and manuscript preparation. Desmond Brown, MD, PhD – literature review and manuscript preparation. Michael J. Link, MD – data analysis, interpretation, and manuscript revision. Nadia N. Laack, MD – interpretation and manuscript revision. David M. Routman, MD – data analysis, interpretation, and manuscript revision. Bruce E. Pollock, MD – data acquisition, interpretation, and manuscript revision. Ian Parney, MD, PhD – conception/design, data acquisition, analysis, interpretation, literature review, and manuscript preparation/revision.

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