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Fractionated stereotactic radiosurgery for recurrent ependymoma in children

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Abstract

Outcomes for children with relapsed ependymoma are poor. Re-irradiation is a potentially viable salvage option in these patients. Data were reviewed for 12 patients (median age 5.6 years) with relapsed ependymoma who received fractionated stereotactic radiosurgery (fSRS) following

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maximal surgical resection from 1995 to 2012. Four patients experienced a second recurrence, including 2 in-field and 2 distant failures. Median time to second recurrence (32 months) was significantly longer than time to first recurrence (24 months) ($p = 0.008$). Three-year local control was 89 %, and median event free survival from fSRS was 3.4 years. Radiation necrosis was observed in 6 patients, 3 who were symptomatic. In conclusion, fSRS offers durable response with a tolerable toxicity profile in children with recurrent EPN.

Keywords

Ependymoma; Stereotactic radiosurgery; Pediatric; Recurrent

Introduction

Ependymoma (EPN) accounts for 6–10 % of pediatric brain tumors. At presentation, current standard initial treatment for EPN in children consists of maximally safe surgical resection, with a goal of gross total resection (GTR), and post-operative standard fractionated radiation therapy (SFRT) to address microscopic residual tumor. With this approach, 5-year overall survival and event free survival (EFS) are 86 and 55 %, respectively [1]. In spite of this high rate of failure, there is no standard of care for recurrent EPN. Given the prognostic significance of GTR in the primary setting and the efficacy of radiation therapy in some, a similar therapeutic approach, though with different radiation techniques, is often employed at relapse. Chemotherapy, though potentially effective short-term, does not offer sustained response at relapse [2, 3]. Several groups have reported on the efficacy of re-irradiation using single-fraction stereotactic radiosurgery (SRS) [4–8], although in some series, there was significant toxicity [7, 8]. Fractionation is one technique to reduce normal tissue toxicity. Based on a linear quadratic model, three fractions of 8 Gy are roughly equivalent to a single fraction of 15 Gy [9]. We utilized fractionated stereotactic radiosurgery (fSRS) with the goal of reducing the risk of radiation necrosis (compared to single fraction SRS) while increasing potency (compared to SFRT). This approach was uniformly implemented at our institution for localized relapse, either within the initially involved site or at a metastatic site. This manuscript serves to update our previously published report [10] on the safety and efficacy of fSRS in relapsed EPN, now with a larger cohort and longer follow up.

Methods

Study Population

Data were retrospectively reviewed for all patients with localized disease at first relapse of EPN treated at Children's Hospital Colorado and the University of Colorado Denver from 1995 to 2012. Clinical data, including patient age, tumor grade, tumor location, extent of surgical resection, and treatment regimen were reviewed. Tumors were measured in the maximal orthogonal dimensions by a single neuro-radiologist. Volumes were estimated by multiplying each measurement and dividing by two. Time to first and second relapse was calculated from the end of each course of radiation. This study was approved by our Institutional Review Board.

Analysis

Descriptive statistics were used for clinical characteristics. Independent variables were compared using the Wilcoxon rank sum test. Local control and overall survival (OS) were estimated using Kaplan–Meier statistics. MATLAB version 7.12 was used for all statistical analyses. Significance was defined as $p < 0.05$.

Results

Between 1995 and 2012, 12 patients with relapsed EPN with localized only disease were treated with fSRS. Initial clinical characteristics of patients at presentation are given in Table 1. Median age at diagnosis was 5.6 years. Eleven patients had disease in the posterior fossa and 1 in the fronto-temporal region. At initial presentation, 2 had subtotal resections (STR), and 10 had GTR, 2 after "second look" surgeries. Chemotherapy was given to all 4 patients with initial STR to allow for second look surgery as previously described [11]. No patients received adjuvant chemotherapy following radiation therapy. Despite second look surgeries, 2 patients had residual disease at the time of SFRT (RT_1). For the majority of patients, RT_1 dose ranged from 55.8 to 59.4 Gy, with the exception of one patient who received 45 Gy due to her young age (1 year old at presentation).

These 12 patients subsequently recurred, with mean time to progression of 24 months (range 1–37 months). Clinical characteristics at recurrence are given in Table 2. Recurrence was at the primary site in 10 and distant (but localized) in 2 patients. Both patients who recurred with distant disease had posterior fossa tumors at diagnosis; 1 recurred in the spine and 1 in the frontal lobe. All patients again underwent maximal surgical resection, which yielded GTR in all, two after multiple surgeries. Both patients with initial STR received chemotherapy between first and second look surgeries. Histologic tumor grade was unchanged for all.

Post-operatively, all patients received fSRS (RT_2). No patients received craniospinal irradiation. Even in the setting of a GTR, our intent was to use adjuvant radiation to treat microscopic disease, similar to the standard of care for initially diagnosed posterior fossa EPN. All patients were treated on a Brainlab Novalis with the Exactrac system (BrainLAB AG, Feldkirchen, Germany) with orthogonal kV imaging for patient alignment. The clinical target volume (CTV) was defined as the tumor bed. A planning target volume (PTV) expansion of 3 mm was used. All patients with recurrences in the previously radiated field received 24 Gy in 3 fractions. Patient 5 recurred outside the initial treatment field and received 30 Gy in 3 fractions. Patient 12 recurred in the original treatment field, which extended down into the cervical spinal cord; she received 25 Gy in 5 fractions to respect spinal cord tolerance. Median time from RT_1 to RT_2 was 25 months. Local control after RT_2 was 89 % at 2 years. Four patients received salvage chemotherapy following re-irradiation. Two received oral low-dose metronomic chemotherapy given high-risk status based on disease recurrence away from their primary site. Two others were treated at other institutions following fSRS and received standard cytotoxic chemotherapy at their clinicians' discretion.

Four patients experienced a second recurrence (2 in the treatment field and 2 distant recurrences in the spine). However, 6 children experienced a longer disease-free period after RT_2 than RT_1, and median time to second progression (32 months; range 5–98 months) was significantly longer than time to first progression ($p = 0.008$) (Fig. 1). At median follow up of 25 months (range 5–98 months), 8 patients were alive with no evidence of disease (NED), and 1 was alive with progressive disease (PD). Two patients died of disease, and 1 patient died of an unrelated cause but had NED at the time of death. Two-year OS following fSRS was 71 %.

Radiation necrosis was defined by typical imaging changes, including contrast enhancement and edema [12] with or without clinical symptoms, followed by resolution of those imaging findings and clinical symptoms. Radiation necrosis occurred in 6 of the 12 patients (50 %), including one patient who received fSRS outside the field of his initial radiation, with median onset of radiographic changes at 5 months (Table 3). Of these six children, only

three required symptomatic management with bevacizumab and steroids. Development of radiation necrosis did not significantly correlate with interval between radiation ($p = 0.56$).

Discussion

Clinical outcomes

Relapsed EPN in children holds a very poor prognosis, with 29 % OS at 2 years [13]. Given the current lack of novel targeted therapies and general inadequacy of systemic chemotherapy for cure, re-operation and re-irradiation are commonly utilized approaches that have been shown efficacious to varying degrees by several groups [4–8].

Single-fraction radiosurgery, which entails a high local dose of radiation given in a single session, has been used in both children and adults with relapsed EPN, especially for inoperable tumors. Stafford et al. [4] published data on 12 pediatric and adult patients (17 total tumors) who underwent SRS for relapsed EPN and reported 68 % local control at 3 years and median survival of 3.4 years. Two patients experienced distant recurrence. Stauder et al. [5] utilized SRS in lieu of re-resection in 26 pediatric and adult patients and estimated 66 % EFS and 69 % OS at 3 years. Local control was achieved in 67 % of patients, with median time to in-field failure of 14.7 months. Distant recurrence occurred in 27 % of patients. Kano et al. [6] published a report of 21 pediatric patients (32 total tumors) for whom local control was achieved in 72 % at 27.6 months. However, the rate of distant tumor relapse was very high at 80.3 %, and 3-year OS was correspondingly low at 23 %. Merchant et al. [7] reported similarly dismal results amongst 6 pediatric patients treated with SRS at relapse, only 1 who survived long-term. Two patients recurred locally at 6.3 and 11.9 months, and 2 patients recurred locally and distally at 8.3 and 18.5 months.

Twelve patients in this cohort received re-irradiation with fSRS (median 24 Gy) at relapse, and 9 were alive at a median follow up of 25 months. With in-field failure in 2 patients at 13 and 98 months, median local control after fSRS was 6 years. Of particular note, is the disease-free interval after fSRS. The typical pattern of relapse often occurs with progressively shortening disease-free intervals. In our series, six of 12 patients currently have a longer disease-free interval after fSRS than their initial disease-free interval. This finding particularly supports the use of fSRS in EPN given the propensity for local recurrence following standard therapy. Two patients experienced distant recurrence following fSRS, which represents a consistent hurdle in the treatment of relapsed EPN and begs the development of novel agents to address therapeutic control throughout the central nervous system.

Toxicity

While many series have reported modest toxicity with reirradiation with SRS, two groups found significant toxicity with SRS. The St. Jude experience saw radiation necrosis in all 6 patients who received SRS for relapsed EPN, including one who died secondary to radiation necrosis of the brainstem [7]. Hodgson et al. [8] reported a high rate of radiation necrosis necessitating re-operation in 19 of 90 patients who received SRS for various relapsed and residual pediatric brain tumors. Given the potential for significant toxicity, we chose to use a fractionated SRS approach for re-irradiation to minimize the risk of signifi-cant radiation necrosis.

In our cohort, fSRS was acutely well tolerated, with only mild fatigue and nausea reported. Six patients exhibited radiologic evidence of radiation necrosis at a median of 5 months (range 2–7 months), including one patient who received fSRS outside the RT_1 radiation field. Clinical symptoms, which mainly included headache and balance disturbance, were

seen in 5 of 6 patients who exhibited radiographic evidence of radiation necrosis. Only three necessitated treatment, and all experienced prompt resolution of symptoms with no long-term morbidity. At the initial presentation of the imaging abnormalities, it is not possible to definitively distinguish radiation necrosis or pseudoprogression from progressive disease without a biopsy, which is not our institutional standard. However, we have sufficient follow up (ranging from 14 to 76 months) to allow the resolution of those imaging findings and clinical symptoms, clarifying the diagnosis of radiation necrosis.

Conclusion

Despite limitations imposed by small sample size, this study supports the role of fSRS as a viable salvage option in children with locally recurrent EPN by offering durable local control, modest toxicity and comparable survival to other forms of salvage therapy.

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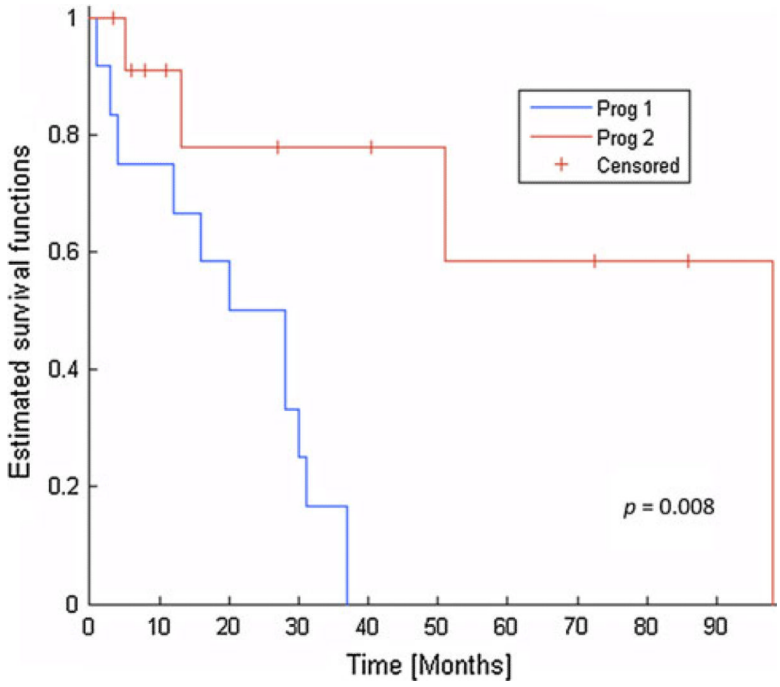

Fig. 1.
Kaplan–Meier analysis showing longer time to second progression than time to first progression

Table 1

Clinical characteristics at presentation

Patient	Age at diagnosis (years)	Tumor size at diagnosis AP × TR × CC (cm)	Surgery	Adjuvent chemotherapy (Yes/no)	Histologic grade (cGy)	Initial RT dose/ # fractions	Time to progression (months)
1	2	3.6 × 3.9 × 5.4	GTR	No[a]	II	5580/31	30
2	7	4.7 × 4.6 × 3.6	GTR	No	III	5940/33	20
3	4	6× 5.3 × 9.2	GTR	No	II	5580/31	28
4	13	3.7 × 4 × 7.5	GTR	No	II	5940/33	31
5	6	3.6 × 2.9 × 5.8	GTR	No	II	5940/33	16
6	1	5.1 × 4.6 × 6.2	GTR	No	II	5940/33[b]	37
7	3	3 × 4.2 × 4.8	STR	No[a]	II	5940/33	3
8	1	4.1 × 5 × 3.5	STR	No[a]	III	4500/25[c]	37
9	6	4.1 × 4.4 × 4.4	GTR	No[a]	III	5940/33	4
10	13	N/A	GTR	No	III	5400/30	28
11	3	6.4 × 5.4 × 6.2	GTR	No	III	5940/33	1
12	14	N/A	GTR	No	III	5400/30	12

STR sub-total resection, *GTR* gross total resection, *AP* anteroposterior, *TR* transverse, *CC* craniocaudal

[a]Patients received chemotherapy between 1st and 2nd look surgeries to reduce tumor size

[b]Patient 6 initially underwent surgery and chemotherapy, and received the initial course of radiation at relapse at age 4

[c]Patient 8 was treated to a lower dose given her young age

Table 2

Clinical characteristics at recurrence

Patient	Tumor size at recurrence AP × TR × CC (cm)	Surgery at recurrence	Salvage chemotherapy	fSRS dose (cGy)/# fractions	Time to 2nd progression (months)	LFU	Current status
1	0.7 × 1 × 0.6	GTR	Yes	2400/3	-	95	NED
2	1.2 × 1.2 × 1	GTR	No	2400/3	13	23	DOD
3	0.8 × 1 × 0.9	GTR	No	2400/3	-	71	NED
4	0.8 × 0.8 × 0.9	GTR	No	2400/3	-	30	Death (unrelated)
5	1.2 × 1.3 × 1.5	GTR	Yes	3000/3	51	76	NED
6	1 × 0.9 × 1.3	GTR	No	2400/3	98	98	PD
7	1.9 × 2 × 2.4	GTR	No	2400/3	5	26	DOD
8	0.9 × 1.7 × 1	GTR	No	2400/3	-	24	NED
9	1.3 × 1.5 × 1.5	GTR	No	2400/3	-	14	NED
10	3.5 × 2.3 × 2.4	GTR	No	2400/3	-	7	NED
11	0.6 × 0.9 × 0.7	GTR	Yes	2400/3		11	NED
12	N/A	GTR	Yes	2500/5		5	NED

STR sub-total resection, *GTR* gross total resection, *NED* no evidence of disease, *DOD* died of disease, *PD* progressive disease, *LFU* last follow up, *AP* anteroposterior, *TR* transverse, *CC* craniocaudal

Table 3

Characteristics of patients with radiation necrosis

Patient	$RT_2 \rightarrow RT$ necrosis by imaging (months)	$RT_2 \rightarrow RT$ necrosis by symptoms (months)	Symptoms	Treatment	Imaging improvement	Symptom improvement
2	5	8	HA, hemiparesis, ataxia	Bevacizumab (5 doses)	18 weeks	6 weeks
3	6	7	Head tilt, nystagmus, ataxia	None	12 weeks	8 weeks
4	7	7	HA, ataxia	None	26 weeks	26 weeks
5	5	N/A	None	None	24 weeks	N/A
7	2	2	HA, ataxia, bilateral CN VI palsy	Bevacizumab (6 doses), Decadron	6 weeks	4 weeks
9	3	5	HA, nystagmus	Bevacizumab (6 doses), Decadron	16 weeks	8 weeks

RT_2 fractionated stereotactic radiosurgery, *RT* radiation, *HA* headache, *CN* cranial nerve