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Stereotactic Radiosurgery for Pediatric and Adult Intracranial and Spinal Ependymomas

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Abstract
Objective/Background: We report efficacy and toxicity outcomes with stereotactic radiosurgery (SRS) for intracranial and spinal ependymoma. ***Methods:*** We analyzed adult and pediatric patients with newly diagnosed or recurrent intracranial or spinal ependymoma lesions treated with SRS at our institution. Following SRS, local failure (LF) was defined as failure within or adjacent to the SRS target volume, while distant failure (DF) was defined as failure outside of the SRS target volume. Time to LF and DF was analyzed using competing risk analysis with death as a competing risk. Overall survival (OS) was calculated from the date of first SRS to the date of death or censored at the date of last follow-up using the Kaplan-Meier method. ***Results:*** Twenty-one patients underwent SRS to 40 intracranial ($n = 30$) or spinal ($n = 10$) ependymoma lesions between 2007 and 2018, most commonly with 18 or 20 Gy in 1 fraction. Median follow-up for all patients after first SRS treatment was 54 months (range 2–157). The 1-year, 2-year, and 5-year rates of survival among patients with initial intracranial ependymoma were 86, 74, and 52%, respectively. The 2-year cumulative incidences of LF and DF after SRS among intracranial ependymoma patients were 25% (95% CI 11–43) and 42% (95% CI 22–60), respectively. No spinal ependymoma patient experienced LF, DF, or death within 2 years of SRS. Three patients had adverse radiation effects. ***Conclusions:*** SRS is a viable treatment option for intracranial and spinal ependymoma with excellent local control and acceptable toxicity.

Introduction

Ependymomas are aggressive tumors that arise from the ependymal cells lining the cerebral ventricles of the brain, the spinal cord central canal, and cortical rests. The standard treatment for intracranial and spinal ependymoma is maximal safe surgical resection. Adjuvant external beam radiotherapy (EBRT) has been shown to prolong survival and delay time to recurrence [1–3].

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Local failure (LF) is the most common type of relapse. Reported incidences of recurrence or progression of intracranial ependymoma at 2 years vary from 20 to 72%, and relapses can occur many years after initial treatment [4, 5]. Important prognostic factors include age at diagnosis, tumor grade, extent of resection, and now molecular factors including *RELA* fusion and chromosome 1q copy number gains [6–12]. At recurrence, various treatment modalities may be used, including repeat surgery when feasible, chemotherapy, additional radiation therapy, and novel treatments through enrollment on clinical trials.

Stereotactic radiosurgery (SRS) is a relatively new modality in the management of ependymoma. SRS allows for precise delivery of high radiation doses with a steep dose drop-off to adjacent normal brain and spine tissue in order to optimize local tumor control while minimizing adverse radiation effects (ARE) to the central nervous system such as radiation necrosis [13] and myelopathy [14]. Frameless image-guided SRS [15] has allowed for treatment of spinal and other extracranial lesions with high accuracy and efficacy [16]. SRS can be used as a primary radiation modality for ependymomas that progress or recur after frontline therapy, or used as boost following EBRT in select cases. However, few studies have reported outcomes for SRS treatment for intracranial and spinal ependymoma, and most are limited by low numbers.

In this study, we report our institutional experience using SRS to treat intracranial and spinal ependymomas. We evaluated local and distant tumor control, overall survival (OS), ARE, and factors correlated with treatment outcomes.

Materials and Methods

Patient Cohort

This retrospective study was approved by the Stanford University Institutional Review Board. Patients were identified through the Stanford Translational Research Integrated Database Environment informatics platform that includes all patients treated at Stanford from 2007 to 2018 [17]. We included adult and pediatric patients with primary or recurrent ependymoma lesions in the brain or spine treated with SRS.

Treatment and Follow-Up Evaluation

Patients were treated with SRS using the CyberKnife (Accuray, Sunnyvale, CA, USA); details of patient immobilization, treatment planning, and target delineation have been previously described [18]. Prescription dose and fractionation were chosen based on tumor size and location as well as history of prior radiation. All SRS treatments were completed in 1–5 fractions on consecutive days in the outpatient setting. Margin around tumor was not added in treatment planning.

Patients were typically evaluated every 3 months after SRS with clinical follow-up and brain and/or spine magnetic resonance imaging (MRI). LF after SRS was defined as radiographic evidence of tumor progression within or adjacent to the SRS target volume. Distant failure (DF) was defined as radiographic evidence of tumor progression outside of the SRS target volume. Distant intracranial failure included occurrence of new lesions in the brain outside of the SRS target volume in intracranial ependymoma patients and development of intracranial metastases in spinal ependymoma patients. Distant spinal failure similarly included occurrence of new spinal lesions outside of the SRS target volume in spinal ependymoma patients and development of spinal metastases in intracranial ependymoma patients. Extraneural metastasis was defined as metastasis outside of the central nervous system. Toxicities and ARE were determined from clinic notes by the treating physician in combination with imaging reports. ARE were distinguished from LF by stabilization or ultimate shrinkage of the lesion on follow-up MRIs over time and/or by pathologic confirmation of necrosis in the absence of residual tumor in resected lesions.

Statistical Analysis

Time to LF and distant intracranial or spinal failure after SRS was measured from the date of SRS and was analyzed using competing risk analysis with death as a competing risk. For patients who did not experience death, LF, or DF were censored at the date of last follow-up. OS was calculated from the date of first SRS to the date of death or censoring and analyzed with the Kaplan-Meier method. Data were analyzed per lesion (LF), per SRS course (distant intracranial or spinal failure), and per patient (OS). Factors correlated with outcomes were analyzed with Cox univariate analysis. All tests were two-sided with an alpha value of 0.05. Statistical analyses were performed using SAS v9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient Cohort and Treatment

Between January 2007 and August 2018, 21 patients underwent SRS to 40 intracranial and spinal ependymoma lesions. All lesions were pathologically confirmed except in 1 patient with a myxopapillary ependymoma diagnosed on the basis of radiographic appearance. Median follow-up for all patients after first SRS treatment was 54 months (range 2–157). The median ages at SRS of pediatric (n = 11) and adult (n = 10) patients were 3 years (range 0–19) and 29 years (range 27–62), respectively. Online supplementary Table e1 and e2 (see www.karger.com/doi/10.1159/000502653 for all online suppl. material) show baseline patient, lesion, and treatment characteristics. Fractionation regimens used are provided in online supplementary Table e3. Representative SRS brain and spine ependymoma plans are shown in online supplementary Figure e1.

In total, 7 patients had SRS to 10 spinal lesions and 16 patients had SRS to 30 intracranial lesions. Of the 15 patients who initially presented with intracranial ependymoma, all underwent surgery and EBRT either adjuvantly or following re-resection for recurrence. One patient received an SRS boost following EBRT. Following EBRT, 8 patients developed isolated LF, 5 patients developed distant intracranial failures, and 1 patient developed both local and distant intracranial failures, all of whom were treated with SRS. One patient developed isolated distant spinal failures treated with spinal EBRT and SRS boost. Of the 6 patients who initially presented with spinal ependymoma, none had neurofibromatosis and all underwent surgery except 1 patient who declined surgery but had radiographic features consistent with myxopapillary ependymoma. The patients who underwent surgical resection did not receive adjuvant EBRT and subsequently developed LFs and distant intracranial and spinal failures that were treated with SRS, as well as EBRT, WBRT (whole-brain radiation therapy), and/or CSI (craniospinal irradiation) for some patients.

Local Failure

Of the 40 total lesions treated, the 2-year cumulative incidence of LF after SRS was 18.5% (95% confidence interval [CI] 8.0–32.5; online suppl. Fig. e2]. The 2-year cumulative incidences of LF of intracranial and spinal lesions were 25.4% (95% CI 10.9–42.8) and 0.0% ($p = 0.21$), respectively. Five patients who underwent SRS for intracranial lesions developed LF, and each underwent a second SRS treatment. Two patients have had no evidence of progression. Three patients developed further local progression after the second SRS treatment. One patient was treated with chemotherapy only and 1 patient was treated with resection only. The third patient had a third SRS treatment but experienced LF 1 month later that was treated again with a fourth SRS treatment. The patient then developed local and distant intracranial failures 9 and 6 months later, respectively, that was further treated with chemotherapy, resection, and CSI. All 3 patients have died from intracranial progression. No spinal lesion failed in the first 2 years and only 1 patient had LF 70 months after SRS, which was treated with resection and chemotherapy. The patient died from disease 6 months after LF. Higher grade (hazard ratio [HR] 6.89, $p = 0.002$) and supratentorial location (HR 6.5, $p = 0.005$) were associated with a higher rate of LF. Male (HR 2.3, $p = 0.18$), single fraction equivalent dose (SFED; HR 1.1, $p = 0.13$), planning target volume (PTV; HR 1.0, $p = 0.78$), and age at diagnosis (HR 1.0, $p = 0.67$) were not associated with LF.

Distant Failure

Of 35 SRS courses analyzed for DF (29 courses to intracranial lesions, 6 to spinal lesions), the 2-year cumulative incidence of DF after SRS was 33.8% (95% CI 18.0–50.3; online suppl. Fig. e3A). The 2-year cumulative incidences of DF after SRS to intracranial and spinal lesions were 41.7% (95% CI 22.3–60.0) and 0.0% ($p = 0.12$), respectively. Only 1 patient who had SRS to spinal lesions developed multiple distant intracranial failures at 51 months later (treated with another course of SRS). The patient then developed further local and distant intracranial and spinal failures 4 months later that were managed with supportive care and died after 2 months. Overall, 19 SRS courses targeted local recurrences only after initial treatment, while 16 SRS courses targeted distant and/or local recurrences (online suppl. Fig. e3B). Nine of the 16 SRS courses to distant recurrences targeted distant intracranial ($n = 8$) and spinal ($n = 1$) recurrences in intracranial ependymoma patients, while the other 7 SRS courses targeted distant spinal ($n = 2$) and intracranial ($n = 5$) recurrences in spinal ependymoma patients. The 2-year cumulative incidence of DF after SRS to local and distant recurrences were 24.0% (95% CI 6.9–46.5) and 45.0% (95% CI 19.2–68.0, $p = 0.26$), respectively. Supratentorial location (HR 6.7, $p = 0.007$) was associated with a higher rate of DF. Higher grade (HR 0.6, $p = 0.28$), female (HR 1.4, $p = 0.6$), and age at diagnosis (HR 1.0, $p = 0.41$) were not associated with DF significantly.

OS and Extraneural Metastasis

Median follow-up for all patients after first SRS treatment was 54 months (range 2–157). The 1-year, 2-year, and 5-year OS of all patients were 90.0% (95% CI 65.3–97.4), 74.1% (95% CI 48.4–88.3), and 67.3% (95% CI 40.8–84.0), respectively. The 1-year, 2-year, and 5-year OS of intracranial ependymoma patients were 85.6% (95% CI 53.3–96.2), 62.2% (95% CI 31.5–82.3), and 51.9% (95% CI 21.7–75.4), respectively. No spinal ependymoma patient died within 5 years; 2 spinal ependymoma patients died at 61 months and 86 months after SRS. One patient developed extraneural metastasis after SRS. This was a pediatric patient with a left frontoparietal anaplastic intracranial ependymoma initially treated with multiple resections and EBRT. The patient then developed distant intracranial failure that was treated with SRS. Two months after SRS, the patient developed extraneural metastasis to lymph nodes and bones, and died 16 months later.

Adverse Radiation Effect

One pediatric patient had pathologically confirmed radiation necrosis. The patient had a left ventricular grade II

ependymoma that was initially treated with STR, followed by GTR for first local recurrence, and GTR and postoperative EBRT (54 Gy in 30 fractions; equivalent dose [EQD_2] 53.1 Gy) for second local recurrence. At third local recurrence, the lesion was treated with a fourth resection (GTR) followed by SRS (18 Gy in 1 fraction) to the resection cavity, with pathology showing grade III anaplastic ependymoma with necrosis. The total EQD_2 of EBRT and first SRS was 95.1 Gy. Eight months after SRS, MRI showed possible tumor recurrence and resection of the lesion showed radiation necrosis without residual tumor. The patient was treated with three more courses of SRS, another STR with postoperative CSI (36 Gy with boost to surgical bed to 54 Gy) upon multiple subsequent LFs.

Two pediatric patients experienced toxicities that may have been related to SRS or combined total RT dose. One underwent GTR of a posterior fossa grade II ependymoma followed by EBRT to the resection cavity (59.4 Gy in 33 fractions; EQD_2 58.4 Gy). Two years later, the patient experienced a local relapse in the prepontomedullary space and was treated with SRS (27.5 Gy in 5 fractions; EQD_2 35.5 Gy). Three months later, the patient had a distant relapse in the right frontal lobe and underwent GTR followed by CSI to 36 Gy with tumor bed boost to 54 Gy. Nine months later, the patient experienced local recurrence in the right frontal lobe resection cavity and was treated with GTR followed by SRS (27 Gy in 3 fractions; EQD_2 42.8 Gy). While the patient remains free of disease at 6 months following the last SRS course, she developed spastic left hemiplegia with increased tone at the left ankle, bilateral foot drop treated with ankle-foot orthosis, and moderate ataxia since CSI, but ataxia did not continue to worsen with more radiation. The other patient underwent STR of a posterior fossa grade III ependymoma followed by chemotherapy. The patient experienced LF 16 months later and underwent STR followed by EBRT to the posterior fossa resection cavity (59.4 Gy in 33 fractions; EQD_2 58.4 Gy). The patient again had LF 1 year later and was treated with near total resection followed by chemotherapy. The patient demonstrated progressive disease on follow-up MRI and was treated with SRS to three lesions in the postoperative cavity (25 Gy in 5 fractions; EQD_2 31.3 Gy). Three months after SRS, imaging showed evidence of necrosis, though the clinical status of the patient had improved from prior to SRS. 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, though necrosis could not be excluded. Eight months after SRS, the patient developed worsening ataxia and right facial weakness, and imaging showed what was interpreted as an admixture of progressive tumor, necrosis, and residual blood products. The patient died 3 months later.

All toxicities occurred in intracranial ependymoma patients under 10 years of age and occurred in previously radiated fields with SFED of SRS >16 Gy and PTV >1.5 cm^3. No patient experienced myelopathy following spinal SRS.

Discussion

Our study represents one of the largest series on SRS treatment for intracranial and spinal ependymomas, with follow-up (median 54 months) longer than most other studies. We show that SRS is a viable treatment option for both adults and children with intracranial or spinal ependymomas.

Ependymomas are aggressive tumors that can recur both locally and distantly following initial treatment. Intracranial ependymomas typically occur during early childhood, while spinal ependymomas more commonly occur in adulthood [19]. Intracranial ependymomas can present in the posterior fossa or in the supratentorial brain. The 5-year progression-free survival and OS are 67 and 89%, respectively, for intracranial ependymoma, and 74 and 91%, respectively, for spinal ependymoma [20, 21]. Gross total resection is associated with better outcomes for both intracranial and spinal ependymoma [22], and EBRT is an important adjuvant treatment for reducing tumor recurrence and improving survival [23, 24]. At recurrence, treatment options are limited. Chemotherapy may be given in the setting of progressive disease but its benefit is unclear [25]. Surgery is often not possible, and repeat EBRT is associated with the risk of radiation necrosis and radiation myelitis [26, 27]. While CSI may improve disease control compared to local field EBRT due to broader radiation fields [28, 29], it is also associated with higher rates of long-term adverse effects such as hearing and cognitive impairment and an increased risk for secondary malignancies [30, 31]. SRS has the benefit of minimizing radiation dose and injury to normal tissue [32–34], which is especially important for pediatric patients who are particularly susceptible to adverse effects associated with radiation injury [28, 35]. Compared to EBRT, SRS has been associated with improved in-field disease control and reduced toxicity [36], but radiation necrosis and other adverse effects can still occur depending on tumor volume, location, and prior history of radiation. Furthermore, SRS, like other focal radiotherapeutic modalities such as EBRT, may be limited in its abil-

ity to control tumor progression outside the narrow treatment field.

To date, there have been few studies evaluating SRS for intracranial and spinal ependymoma, and survival, tumor control, as well as ARE vary widely by institutions (online suppl. Table e4) [37]. Our study attempts to address the need for additional clinical evidence to understand the impact of SRS on tumor control and ARE. In a recent multicenter study involving 89 patients with recurrent intracranial ependymoma treated with Gamma Knife SRS [38], 1-year local control, distant control, and OS were 71, 75, and 86%, respectively, compared to the intracranial ependymoma cohort in our study showing 82, 67, and 86%, respectively. Worse local tumor control in the multi-institutional cohort may be due to a lower median SRS dose (13–15 Gy compared to 18 Gy in our study) and included a greater proportion of grade 3 ependymomas, which have poorer prognoses.

Consistent with previous results, DF was higher following SRS among patients with intracranial ependymoma and those with distant recurrences after initial treatment, though not statistically significant due to low numbers. We also found that patients with distant recurrences treated with SRS were numerically more likely to fail distantly (HR 1.8, $p = 0.26$). This data supports selecting SRS in particular for the subset of patients with spinal and locally recurrent ependymoma.

We found that LF was higher following SRS among intracranial ependymoma lesions compared to spinal ependymoma lesions, likely reflecting a different biology between the two [39]. Supratentorial location, for example, is associated with certain unfavorable mutations (e.g., RELA) [40]. In addition, the intracranial lesions in our series were more likely to be recurrences in previously irradiated areas (14 out of 16) compared to the majority of spinal ependymoma lesions which arose in unirradiated regions (8 out of 10). Therefore, the intracranial ependymoma lesions included in this study may have been more treatment- and radiation-resistant.

In contrast to our findings, in a previous study of 6 pediatric patients treated with SRS re-irradiation for recurrent intracranial ependymoma showed, only 1 achieved disease control, 4 died from disease progression, and 1 died from radiation necrosis [29]. The greater incidence of radiation necrosis in this study may be due to the fact that 5 of 6 patients received SRS re-irradiation to sites that were included in the high-dose volume of previous radiation. In contrast, in our study, only 7.5% of intracranial ependymoma lesions received prior radiation at the site of SRS, and our ARE rates for intracranial ependymoma lesions were only 10%. While SRS has been shown to be less effective in the setting of previously treated ependymoma lesions, management of these tumors is incredibly difficult and most alternative strategies do not lead to durable survival benefits.

This study has several limitations. First, the number of patients is low given the rarity of ependymoma and limited our ability to perform subgroup analyses, but was larger than all other single institutional studies (online suppl. Table e4). Genomic profiling of clinically significant alterations, such as PFA/PFB among posterior fossa ependymoma and YAP1 fusions, was also not available for the patients in our study [41]. Additionally, differentiating local recurrence and ARE can be difficult which may lead to misclassification in our study [42, 43]. Finally, follow-up time for some patients was short, and extended monitoring is necessary to more accurately estimate rates of long-term toxicity and tumor control.

In conclusion, SRS is an effective and safe method to treat intracranial and spinal ependymoma. Patterns of recurrence (distant vs. local) and biological subtyping [12] will be increasingly important in the future to guide an appropriate treatment selection [35].

Statement of Ethics

This study was approved by the institutional research committee and is in accordance with the 1964 Helsinki Declaration and its later amendments.

Disclosure Statement

The authors have no conflicts of interest to declare.

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