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Stereotactic Radiosurgery for Ependymoma in Pediatric and Adult Patients: A Single-Institution Experience

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BACKGROUND AND OBJECTIVES: Ependymoma is commonly classified as World Health Organization grade 2 with the anaplastic variant categorized as grade 3. Incomplete resection or anaplastic features can result in unfavorable outcomes. Stereotactic radiosurgery (SRS) provides a minimally invasive approach for recurrent ependymomas. Our study investigates the efficacy and safety of SRS for grade 2 and 3 ependymomas in pediatric and adult populations.

METHODS: We conducted a retrospective analysis on 34 patients with 75 ependymomas after CyberKnife SRS between 1998 and 2023. Fourteen were pediatric (3-18 years), and 20 were adult (19-75 years) patients. The median age was 21 years, and the median tumor volume was 0.64 cc. The median single-fraction equivalent dose was 16.6 Gy, with SRS administered at 77% of the median isodose line.

RESULTS: After a median follow-up of 42.7 months (range: 3.8-438.3), 22.7% of ependymomas progressed. The 5-year local tumor control rate was 78.1%, varying between 59.6% and 90.2% for children and adults, with grade 2 at 85.9% compared with 58.5% for grade 3 tumors. The 5-year overall survival rate was 73.6%, notably higher in adults (94.7%) than in children (41%), and 100% for grade 2 but decreased to 35.9% for grade 3 patients. The 5-year progression-free survival rate was 68.5%, with 78.3% and 49.2% for adults and children, respectively, and a favorable 88.8% for grade 2, contrasting with 32.6% for grade 3 patients. Symptom improvement was observed in 85.3% of patients. Adverse radiation effects occurred in 21.4% of pediatric patients.

CONCLUSION: Our study supports SRS as a viable modality for pediatric and adult patients with grade 2 and 3 ependymomas. Despite lower local tumor control in pediatric and grade 3 cases, integrating SRS holds promise for improved outcomes. Emphasizing careful patient selection, personalized treatment planning, and long-term follow-up is crucial for optimal neurosurgical outcomes.

KEY WORDS: Stereotactic radiosurgery, CyberKnife radiosurgery, Ependymoma

Ependymomas are malignant neoplasms originating from ependymal cells lining cerebral ventricles, spinal cord central canal, and cortical rests.[1] In adults, infratentorial and spinal ependymomas are diagnosed at nearly equal rates, while pediatric cases predominantly involve infratentorial locations.[2] Histologically, ependymomas are classified as World Health

ABBREVIATIONS: ARE, adverse radiation effect; **BED,** biologically effective dose; **EBRT,** external beam radiotherapy; **EQD2,** equivalent total doses in 2-Gy fractions; **LTC,** local tumor control; **OS,** overall survival; **SFED,** single-fraction equivalent dose; **SRS,** stereotactic radiosurgery; **WHO,** World Health Organization.

Organization (WHO) grade 2, whereas anaplastic ependymomas are grade 3.[3]

Standard management involves maximal safe surgical resection,[4] with adjuvant external beam radiotherapy (EBRT) enhancing survival and local tumor control (LTC).[5] Incomplete removal and anaplastic features indicate poorer prognosis,[6] often leading to challenging management upon recurrence, necessitating additional interventions or chemotherapy.[7]

Stereotactic radiosurgery (SRS) is a minimally invasive treatment modality,[8-11] delivering precise high-dose radiation. SRS optimizes LTC while minimizing adverse radiation effects (ARE), such as radiation necrosis[12] and myelopathy.[13] SRS can be used as a primary radiation modality for recurrent or progressive ependymomas or as a boost subsequent to EBRT.[14] The advent of frameless image-guided SRS has revolutionized the treatment of spinal and other extracranial lesions because of its exceptional accuracy and efficacy.[15] However, the available literature on SRS outcomes for intracranial and spinal ependymomas in both pediatric and adult patients remains scarce with limited sample sizes.[16-23]

This study evaluates the efficacy and safety of CyberKnife SRS in treatment of intracranial and spinal ependymomas of WHO grade 2 and 3. Encompassing both pediatric and adult populations, it represents the largest single-institution, long-term experience.

METHODS

Patient Characteristics

Between 1998 and 2023, 34 patients with 75 ependymomas underwent CyberKnife SRS. Patient selection was based on a follow-up period exceeding 3 months, with clinical data securely stored in an IRB-approved database following the Helsinki Declaration. All participants consented to the use of their data for research aimed at improving future patient care. Data can be requested from the first author, KHY, but are not publicly accessible to comply with the Health Insurance Portability and Accountability Act, ensuring patient information and privacy protection.

Demographic characteristics are outlined in Table 1. The study comprised 14 (41.2%) pediatric patients (ages 3-18) and 20 (58.8%) adults (ages 19-75), with a median age at SRS of 21 years, 8 years (range: 4-17) for children and 32.5 years (range: 19-65) for adults. Surgery preceded SRS in 28 (82.3%) patients overall, with 12 (85.7%) pediatric and 16 (80%) adult patients. Ependymomas were histologically classified as WHO grade 2 or 3.[24] Two pediatric and 4 adult patients received SRS as primary treatment based on radiographic diagnosis, with grading determined by radiologic morphology. Symptoms correlated with lesion location (Table 1).

Tumor Characteristics

The median tumor volume measured 0.64 cc (mean: 1.8; range: 0.03-17.5). Among the 75 lesions, 31 (41.3%) occurred in pediatric patients and 44 (58.7%) in adults. Of these, 46 (61.3%) were classified as grade 2 and 29 (38.7%) as grade 3. Predominant lesion locations included ventricular (n = 15, 20%), cerebellar (n = 10, 13.3%), and frontal (n = 8, 10.7%). Lesion entities were classified as primary (n = 2, 2.7%), residual (n = 11, 14.7%), recurrent (n = 60, 80%), and metastatic (n = 2, 2.7%, Table 1). Metastatic presentations of ependymoma were accompanied by leptomeningeal disease at the onset of SRS.

Treatment

Cranial and spinal ependymomas underwent CyberKnife SRS (Accuray, Inc.) following the method by Shi et al[1] (Figure 1). The median time from diagnosis to SRS was 75.8 months (range: 1-367.4). The median target volume for the entire cohort was 0.6 cc (range: 0.03-17.5 cc), with children at 0.3 cc (range: 0.3-17.5) and adults at 0.9 cc (range: 0.03-13.6). SRS was delivered with a median single-fraction equivalent dose (SFED) of 16.6 Gy to the 77% median isodose line (range: 48-94). Notably, there were no significant differences in marginal dose, maximum dose, isodose line, and number of fractions between pediatric and adult groups (Table 2).

The biologically effective dose (BED) for each lesion was computed using the linear-quadratic model,[25] with an α/β ratio of 3 Gy to accommodate benign cell repair capability.[26] These BED values were then converted to SFED and equivalent total doses in 2-Gy fractions (EQD2) for comparative analysis using linear-quadratic model.[27] Across the entire cohort, the median BED was 108 Gy (range: 26.7-660), the median SFED was 16.6 Gy (range: 7.6-43), and the median EQD2 was 64.8 Gy (range: 16-396) for treated lesions (Table 2). Notably, BED, SFED, and EQD2 showed no significant differences between the groups.

Follow-Up

Patients underwent clinical evaluation and MRI follow-up twice annually during the initial 2 years post-SRS, followed by annual evaluations. Tumor volume was measured in axial, sagittal, and coronal planes by multiplying dimensions and dividing the product by 2. Statistical analysis employed Kaplan-Meier analysis, and graphical representations were generated using standard statistical software (IBM SPSS Statistics 29.0) and Origin 2023.

RESULTS

After excluding patients lost to follow-up, 75 lesions in 34 patients were eligible for inclusion. Among them, 14 (41.2%) were pediatric and 20 (58.8%) adult patients, with 10 (29.4%) patients passing away during evaluation. Demographic analysis revealed a distinct age-related pattern in ependymoma incidence: grade 2 tumors favored adult onset (84.1%), while grade 3 lesions were more prevalent in pediatric cases (71%, Table 1). The median follow-up after SRS treatment was 42.7 months (range: 3.8-438.3, Table 2).

Local Tumor Control

Among 75 ependymomas, 17 (22.7%) progressed, 6 (8%) regressed, and 52 (69.3%) remained stable in volume. The 5-year LTC (5-year LTC) rate for all ependymomas was 78.1%, with a lower rate of 59.6% observed in the pediatric cohort while a higher rate of 90.2% was seen in adult patients ($P = .03$, Table 3, Figure 2). For ependymomas classified as WHO grade 2, the 5-

TABLE 1. Demographic Characteristics in 34 Patients With 75 Ependymomas

Characteristic	Entire cohort	Pediatric	Adult
No. Patients	34 (100%)	14 (41.2%)	20 (58.8%)
Sex			
Male	20 (59%)	7 (50%)	13 (65%)
Female	14 (41%)	7 (50%)	7 (35%)
Prior surgery			
Single	15 (44%)	2 (14%)	13 (65%)
Multiple	13 (38.2%)	10 (86%)	3 (35%)
Symptoms			
Headaches	10 (25.6%)	4 (25%)	6 (26.1%)
Motor impairment	7 (17.9%)	4 (25%)	2 (8.7%)
Back pain	6 (15.4%)	1 (6.3%)	2 (8.7%)
Vomiting	4 (10.3%)	2 (12.5%)	1 (4.3%)
Dizziness	4 (10.3%)	2 (12.5%)	5 (21.7%)
Seizure	3 (7.7%)	2 (12.5%)	3 (13%)
Sensory deficit	2 (5.1%)	1 (6.3%)	1 (4.3%)
Cranial nerve palsy	2 (5.1%)	0 (0%)	1 (4.3%)
Weight loss	1 (2.6%)	0 (0%)	2 (8.7%)
No. Tumors	75 (100%)	31 (41.3%)	44 (58.7%)
Location			
Ventricular	15 (20%)	11 (35.5%)	4 (9.1%)
Cerebellum	10 (13.3%)	8 (%)	2 (4.5%)
Frontal	8 (10.7%)	3 (9.7%)	5 (11.4%)
Temporal	5 (6.7%)	4 (12.9%)	1 (2.3%)
Cervical	5 (6.7%)	0 (0%)	5 (11.4%)
Thoracal	5 (6.7%)	0 (0%)	5 (11.4%)
Lumbar	5 (6.7%)	0 (0%)	5 (11.4%)
Cerebellopontine	4 (5.3%)	0 (0%)	4 (9.1%)
Cervicomedullary	4 (5.3%)	2 (6.4%)	2 (4.5%)
Carvenous	2 (2.7%)	0 (0%)	2 (4.5%)
Sacral	2 (2.7%)	0 (0%)	2 (4.5%)
Brainstem	2 (2.7%)	2 (6.4%)	0 (0%)
Suprasellar	2 (2.7%)	0 (0%)	2 (4.5%)
Pineal	1 (1.3%)	0 (0%)	1 (2.3%)
Tentorium	1 (1.3%)	0 (0%)	1 (2.3%)
Jugular	1 (1.3%)	1 (3.2%)	0 (0%)
Sellar	1 (1.3%)	0 (0%)	1 (2.3%)
Thalamic	1 (1.3%)	0 (0%)	1 (2.3%)
Parietal	1 (1.3%)	0 (0%)	1 (2.3%)
Clinical presentation			
Symptomatic	70 (93.3%)	30 (96.8%)	40 (90.9%)
Asymptomatic	5 (6.7%)	1 (3.2%)	4 (0.1%)
Entity			
Primary	2	0	2
Residual	11	1	10
Recurrent	60	30	30
Metastatic	2	0	2
Lesion characteristics			
WHO 2	46 (61.3%)	9 (29%)	37 (84.1%)
WHO 3	29 (38.7%)	22 (71%)	7 (15.9%)

WHO, World Health Organization.

year LTC rate was 85.9%, whereas it was 58.5% for those classified as grade 3 (P = .14, Table 3, Figure 3).

Patient Survival

The 5-year overall survival (OS) (5-year OS) rate for all patients was 73.6%. Adult patients demonstrated significantly higher rates of OS (94.7%) compared with pediatric patients (41%) (P < .001, Table 3, Figure 2B). Moreover, when stratifying by the WHO classification, patients with ependymomas classified as grade 2 exhibited a remarkable 5-year OS rate of 100%, whereas it significantly decreased to 35.9% for patients with grade 3 lesions (P < .001, Table 3, Figure 3B).

Progression-Free Survival

The 5-year progression-free survival (PFS) (5-year PFS) rate was 68.5% for all patients, with higher rates observed in adults (78.3%) compared with pediatric patients (49.2%, Table 3, Figure 2C). For patients with WHO grade 2 lesions, the 5-year PFS rate was 88.8%, significantly higher than the rate of 32.6% for patients with grade 3 tumors (P < .001, Table 3, Figure 3C).

Symptomatic Outcome

One (7.1%) pediatric and 4 (20%) adult patients were asymptomatic, allowing a clinical evaluation of symptomatic outcomes for 29 (85.3%) patients with 62 (82.7%) symptomatic

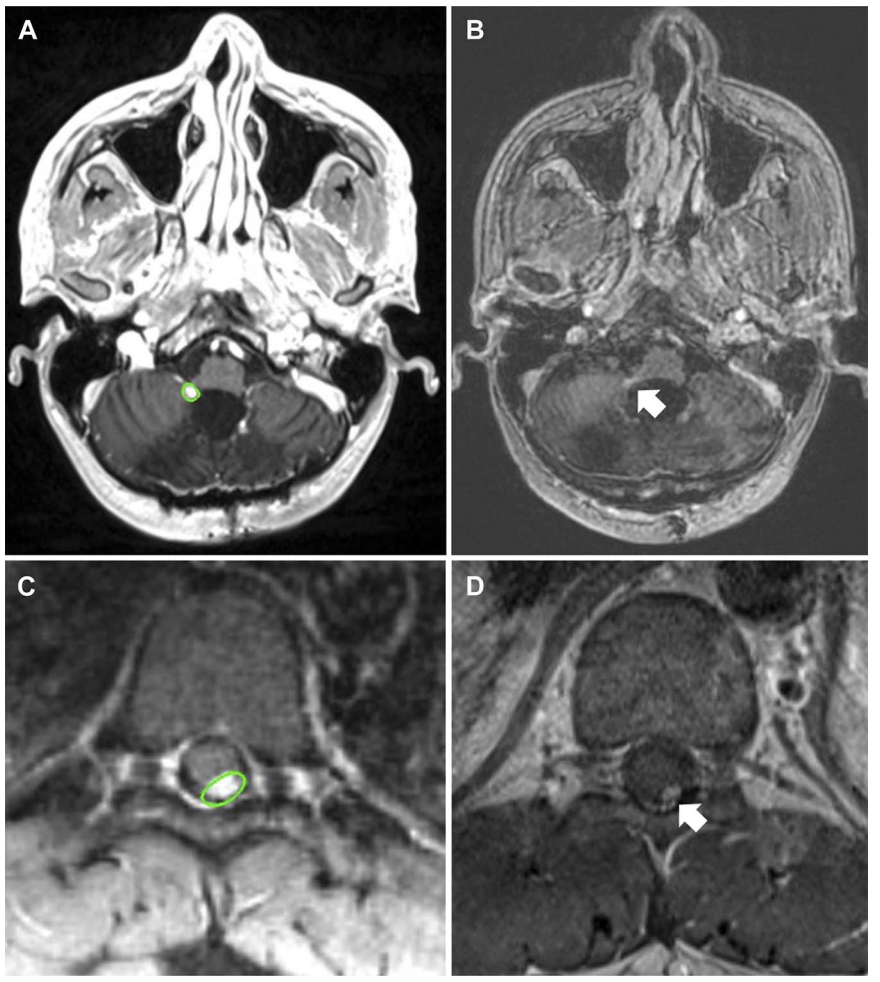

FIGURE 1. *Comparison of baseline CyberKnife treatment plans and subsequent radiographic evaluations for patients with cranial and spinal ependymomas.* **A** *and* **B**, *The initial treatment plans and* **B** *and* **D**, *images from the most recent follow-ups.* **A** *and* **B**, *A 20-year-old male patient diagnosed with multiple recurrent grade 3 ependymoma (EP-PF-A) status post-multiple CyberKnife treatments for the cranial lesions, presented with a recurrent right cerebellar lesion during surveillance.* **A**, *A marginal dose of 27 Gy was delivered with the maximum dose of 35.62 Gy in 3 fractions to 76% of the isodose line.* **B**, *A substantial reduction in tumor size was evident in the 3-month follow-up MRI.* **C** *and* **D**, *A 21-year-old male patient with a history of multifocal myxopapillary ependymoma status postsurgical resection for thoracic and lumbar intradural ependymomas, presented with a new T8 spinal lesion during surveillance.* **C**, *He received CyberKnife treatment with a marginal dose of 24 Gy (maximum dose 32 Gy) in 3 fractions to 75% isodose line.* **D**, *A significant decrease in tumor size was observed, with consistent control over the tumor in the 12-year follow-up MRI.*

ependymomas. After SRS treatment, 23 (67.6%) patients demonstrated symptomatic improvements (Table 3). Of them, 10 (71.4%) pediatric patients and 13 (65%) adult patients experienced improvement in their symptoms ($P < .05$). In children, greater improvement was observed in headaches, motor impairment, vomiting, dizziness, and seizures. Conversely, significant improvements were noted in headaches, back pain, motor impairment, cranial nerve palsy, vomiting, and dizziness in adults.

Among the 23 patients with symptomatic improvement, 15 (75%) had grade 2 ependymomas, and 8 (57.1%) had grade 3 ependymomas ($P < .05$, Table 3). Notably, no pediatric patients and only one (5%) adult patient with grade 2 ependymoma experienced worsening of seizure incidence after SRS treatment ($P < .05$, Table 3). Furthermore, 2 (14.3%) children developed new symptoms after SRS ($P < .05$, Table 3).

TABLE 2. Treatment Characteristics in 34 Patients With 75 Ependymomas

Characteristics	Entire cohort	Pediatric	Adult	Statistical significance (*P* values)
No. Tumors per patient				
Mean	2.3	2.6	2.1	.38
Median	2	2	2	
Range	1-9	1-9	1-5	
Age at treatment, y				
Mean	25.3	9.6	36.3	**<.001**
Median	21	8	32.5	
Range	4-65	4-17	19-65	
Interval between diagnosis to SRS, mo				
Mean	104.7	84.5	24.3	
Median	75.8	69	95.2	.15
Range	1-367.4	1-327.2	1.3-367.4	
Target tumor volume, cc				
Mean	1.8	1.4	2.1	.41
Median	0.6	0.3	0.9	
Range	0.03-17.5	0.03-17.5	0.03-13.6	
Margin dose, Gy				
1 fraction				
Mean	18.5	20.2	18.4	
Median	18	20	18	
Range	12-24	18-25	16-24	
2 fractions				
Mean	25	N/A	25	
Median	20	N/A	20	
Range	10-60	N/A	10-60	
3 fractions				
Mean	23.7	24	23.7	.25
Median	24	25.5	24	
Range	18-27	18-27	18-27	
4 fractions				
Mean	N/A	N/A	N/A	
Median	N/A	N/A	N/A	
Range	N/A	N/A	N/A	
5 fractions				
Mean	27.1	26.7	27.5	
Median	27.5	27.5	27.5	
Range	25-30	25-27.5	25-30	

TABLE 2. Continued.

Characteristics	Entire cohort	Pediatric	Adult	Statistical significance (*P* values)
Maximum dose, Gy				
1 fraction				
Mean	23.9	23.8	24.1	
Median	23.6	24.1	22.9	
Range	15.8-32	15.8-31.2	20-32	
2 fractions				
Mean	32.2	N/A	32.2	
Median	25.8	N/A	25.8	
Range	13.3-77.9	N/A	13.3-77.9	
3 fractions				
Mean	31.3	32.2	31	.24
Median	32	33.9	32	
Range	22.5-37.5	23.4-37.5	22.5-35.1	
4 fractions				
Mean	N/A	N/A	N/A	
Median	N/A	N/A	N/A	
Range	N/A	N/A	N/A	
5 fractions				
Mean	37.1	36.7	37.5	
Median	36.4	36.7	36.2	
Range	33.3-42.9	34.3-39.3	33.3-42.9	
# Fraction				
Mean	1.9	1.6	2.1	
Median	1	1	2	.13
Range	1-5	1-5	1-5	
BED, Gy				
Mean	121.4	125	118.9	
Median	108	126	101.3	.73
Range	26.7-660	54-216	26.7-660	
SFED				
Mean	17.1	17.6	16.8	
Median	16.6	18	16	.44
Range	7.6-43	11.3-24	7.6-43	
EQD2				
Mean	72.8	75	71.4	
Median	64.8	75.6	60.8	.7
Range	16-396	32.4-129.6	16-396	
Isodose line, %				
Mean	77.4	77.5	77.3	.8
Median	77	77	76	
Range	48-94	70-85	48-94	

TABLE 2. Continued.

Characteristics	Entire cohort	Pediatric	Adult	Statistical significance (*P* values)
Follow-up, mo				
Mean	88.4	60.5	108	.06
Median	42.7	37	42.7	
Range	3.8-438.3	3.8-313.9	11.8-438.3	

BED, biologically effective dose; EQD2, equivalent total doses in 2-Gy fractions; N/A, not applicable; SFED, single-fraction equivalent dose; SRS, stereotactic radiosurgery.
P values were calculated using the log-rank test, with statistical significance denoted in bold.

Adverse Radiation Effect

One (7.1%) pediatric patient confirmed radiation necrosis. This patient initially had a grade 2 ependymoma in the left ventricle, treated with subtotal resection, followed by gross total resection, EBRT (54 Gy), and SRS (18 Gy) to the resection cavity. Pathology revealed grade 3 anaplastic ependymoma with necrosis. Subsequently, the patient underwent 3 additional SRS courses and another subtotal resection with postoperative craniospinal irradiation because of multiple local failures.

Two (14.3%) pediatric patients experienced toxicities associated with either SRS or cumulative radiation dose. One patient underwent gross total resection, EBRT (59.4 Gy), and SRS (27.5 Gy) for a grade 2 ependymoma, followed by additional GTRs and craniospinal irradiation (36 Gy + 54 Gy boost). Despite initial improvement, neurological symptoms reappeared post-CSI. In the other case, although imaging indicated necrosis post-SRS, the patient's clinical status temporarily improved before a fatal outcome.

All toxicities occurred in pediatric patients with intracranial ependymoma in previously irradiated regions, with SFED exceeding 16 Gy and a planning target volume larger than 1.5 cc.[1] Notably, no patient experienced myelopathy after spinal SRS.

DISCUSSION

Our study represents the largest single-institution evaluation of SRS outcomes for intracranial and spinal ependymomas across pediatric and adult populations. We aimed to provide comprehensive insights into treatment outcomes through long-term follow-up, providing valuable evidence for guiding clinical decision-making in ependymoma management.

TABLE 3. Summary of Patient Outcomes

Variables	Entire series	Pediatric	Adult	Statistical significance (*P* value[a])	Grade 2	Grade 3	Statistical significance (*P* value[a])
LTC							
5 y, %	78.1	59.6	90.2	**.03**	85.9	58.5	.14
Final FU, %	57.9	29.8	70.7		62.4	58.5	
OS							
Rate (5 y, %)	73.6	41	94.7	**<.001**	100	35.9	**<.001**
Final FU (mean, mo)	97.1	60.5	132.5				
PFS							
Rate (5 y, %)	68.5	49.2	78.3	.19	88.8	32.6	**<.001**
Final FU (mean, mo)	110.3	61.4	151.4				
SI, %	67.6	71.4	65	**.04**	75	57.1	**.03**
SW, %	2.9	0	5	**.004**	5	0	**.004**
NS, %	5.9	14.3	0	**.01**	5	7.1	.06

FU, follow-up; LTC, local tumor control; NS, new symptoms; OS, overall survival; PFS, progression-free survival; SI, symptomatic improvement; SW, symptomatic worsening.
[a]*P* values were calculated using log-rank test, with statistical significance denoted in bold.

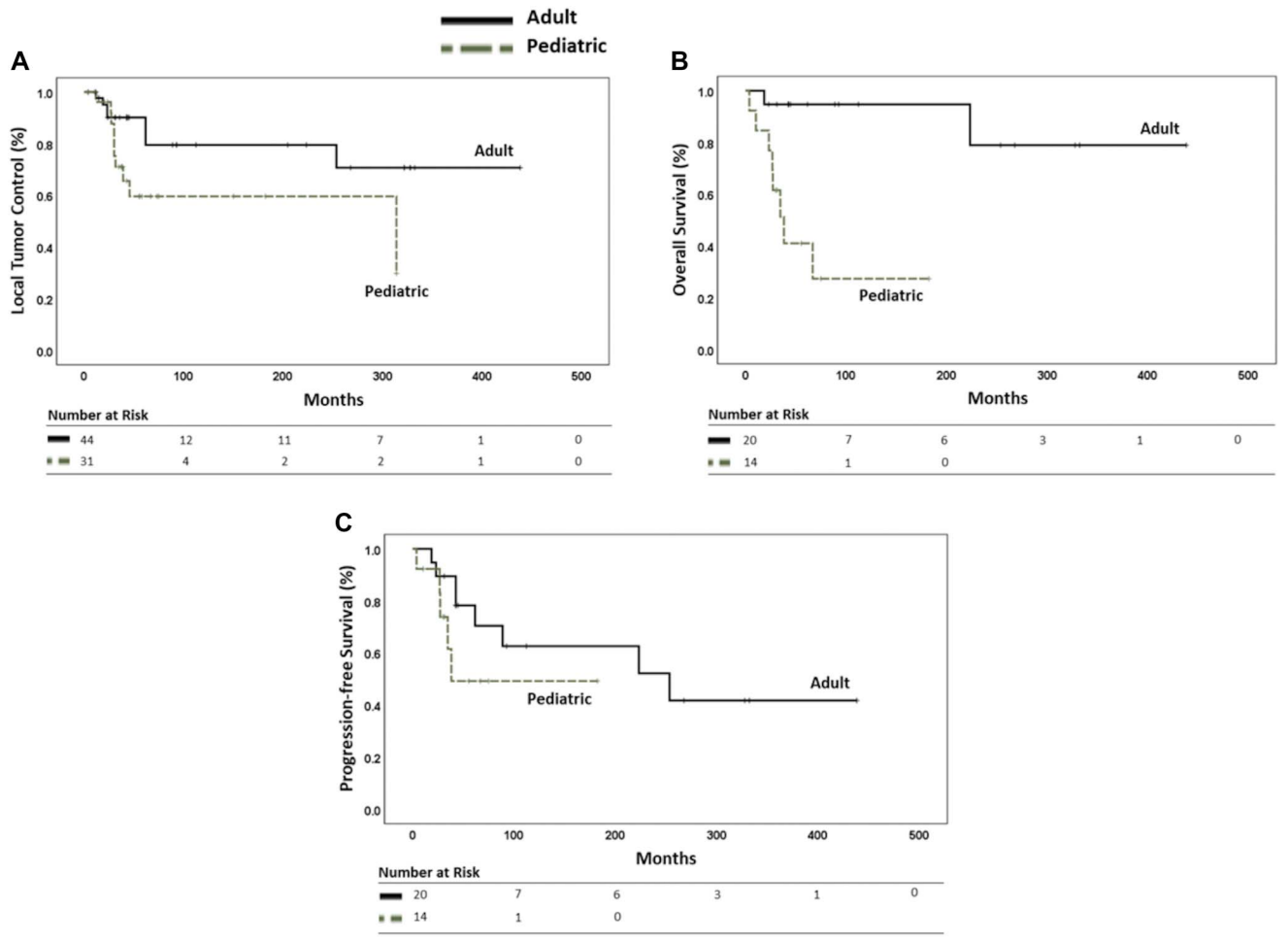

FIGURE 2. *Overview of patient outcomes with a comparative analysis between pediatric (green, dashed) vs adult (black, solid) populations based on the Kaplan-Meier method with number of lesions and patients at risk. The specific outcome parameters evaluated are as follows:* **A**, *Local tumor control rate (P = .03);* **B**, *overall survival rate (P < .001); and* **C**, *progression-free survival rate (P = .19).*

Demographics and Treatment Characteristics

We analyzed 34 patients with a median age of 21 years, demonstrating the efficacy of SRS in managing WHO grade 2 and 3 ependymomas. Our findings revealed a smaller median tumor volume (0.64 cc) and a higher median SFED of 16.6 Gy compared with the literature's median margin dose of 15 Gy and tumor volume of 2.2 cc.[28] In addition, we observed a significant disparity in the median period from diagnosis to SRS initiation. For primary and residual lesions, the median interval was 4.6 months, while for recurrent lesions, it extended to 77.5 months ($P < .001$), emphasizing the importance of timing in treatment decisions, especially in recurrent cases.

The extended duration of our study allowed for a comprehensive examination of the interaction between diverse treatment modalities and patient outcomes, revealing a correlation between multimodal therapy and compromised LTC and/or PFS.

Our study depicted advancements in fractionation techniques and chemotherapy regimens. Analysis based on BED, SFED, and EQD2 revealed that toxicities were predominantly observed in pediatric patients with intracranial ependymomas in previously irradiated regions, particularly when SFED exceeded 16 Gy and the planning target volume surpassed 1.5 cc. This underscores the multifaceted nature of patient tolerance to SRS, influenced by diverse factors including demographics, comorbidities, predispositions, concurrent therapies, and treatment compliance.

The integration of SRS into multimodal treatment regimens alongside conventional therapies presents both opportunities and challenges in optimizing patient outcomes. This emphasizes the significance of personalized treatment strategies tailored to individual patient profiles and disease characteristics, supported by evidence-based interventions and clinical expertise.

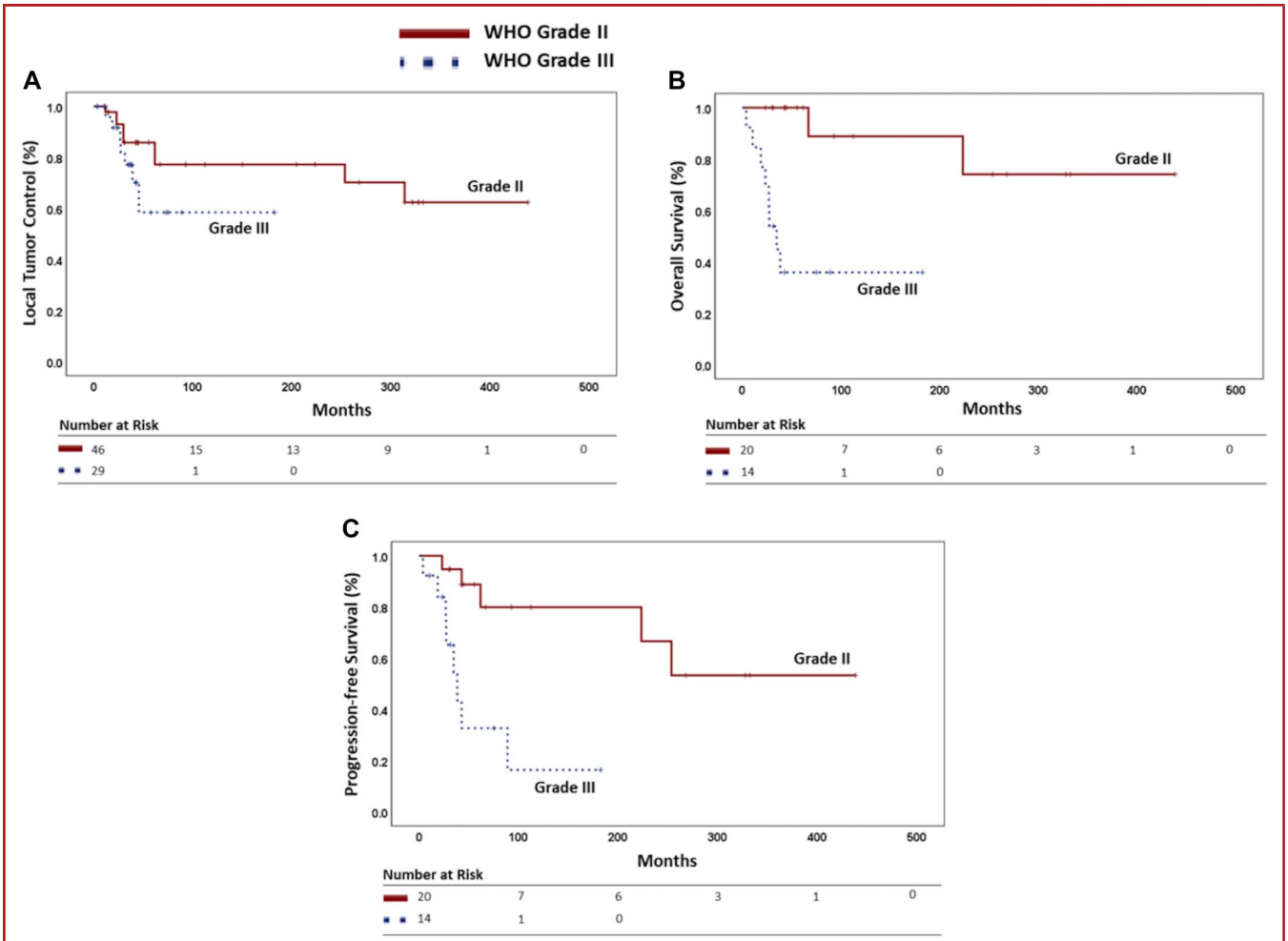

FIGURE 3. *Overview of patient outcomes in relation to comparative analysis between WHO grade 2 ependymomas (red, solid) vs grade 3 lesions (blue, dashed) utilizing the Kaplan-Meier method with number of lesions and patients at risk. The specific outcome parameters evaluated are as follows:* **A**, *Local tumor control rate (P = .14);* **B**, *overall survival rate (P < .001); and* **C**, *progression-free survival rate (P < .001).WHO, World Health Organization.*

LTC, OS, PFS, and Symptomatic Outcomes

Our study identified significant disparities in LTC, OS, PFS, and symptomatic outcomes based on age and tumor grade. We observed an improved 5-year OS rate of 73.6%, surpassing the 44% reported in previous literature (Table 4).[6,28-38] There were substantial discrepancies in OS rates between adult (94.7%) and pediatric (41%) cohorts, underscoring the importance of age-related considerations in treatment outcomes ($P < .001$). These findings underscore the intricate relationship between age, tumor biology, treatment response, and overall health.[39]

LTC is crucial for optimizing patient outcomes and quality of life.[40] Our study demonstrated a promising 5-year LTC rate of 78.1% across all ependymomas, consistent with previous literature.[28] However, concerns arose with a lower 5-year LTC rate of 59.6% in pediatric patients compared with adults (90.2%, $P = .03$). Moreover, grade 2 ependymomas exhibited a notably higher 5-year LTC rate (85.9%) compared with grade 3 tumors (58.5%). These findings underscore variances in LTC rates across diverse patient demographics and tumor characteristics, indicating potential challenges in achieving LTC with SRS in pediatric patients and higher-grade ependymomas.[28]

PFS represents a critical end point,[14] and our study demonstrated achievements in this area. While previous literature indicated a 5-year PFS rate of 48%,[28] our study revealed a notably higher rate of 68.5%, with distinct outcomes based on tumor grade. Patients with grade 2 ependymomas exhibited a significantly higher 5-year PFS rate of 88.8% compared with grade 3 tumors ($P < .001$). These findings suggest that SRS may be more effective in preventing disease progression in adult patients and those with lower-grade tumors.[41]

TABLE 4. Comprehensive Review of Pertinent Studies on Stereotactic Radiosurgery for Intracranial and Spinal Ependymomas

Author (y)	No. Pat.	No. Lesions	Median dose (Gy)	Median fraction	Tumor volume (cc)	Median FU (mo)	OS/PFS	ARE (no./%)	Local/distal failure
Shi et al (2019)[1]	IC: 15 SP: 6	IC: 3 SP: 10	IC: 20 SP: 10	IC: 1 SP: 2	IC: 0.95 SP: 0.74	45.5	89.4/90 (1 y) NR/67.3 (5 y)	3/14.3	18.5/33.8 (2 y)
Elibe et al (2018)[30]	SP: 2	NR	SP: 16	SP: 1	Findings reported amidst diverse non-ependymoma spinal pathologies				
Kano et al (2018)[28]	IC: 89	IC: 113	IC: 15	IC: 1	IC: 2.2	18	86/71 (1 y) 44/48 (5 y)	9/10	37/NR (last FU) NR/61(1 y) NR/85 (5 y)
Lobón et al (2016)[31]	IC: 8	IC: 8	IC: 35	IC: 8	NR	32.5	75/NR (1 y) 50/NR (3 y) NR/30.6 (mo)	2/25	25/37.5
Murai et al (2016)[32]	IC: 8	IC: 38	IC: 15.3 (unfr), 23 (fr)	IC: 1 (unfr), 4 (fr)	IC: 0.9	IC: 23	100/26 (1 y) 38/21 (3 y)	3/37.5	24/NR (3 y)
Hoffman et al (2014)[33]	IC: 12	IC: 12	IC: 24	IC: 3	IC: 1.4	IC: 25	71/NR (2 y) NR/40 (mo)	6/50	11/86.7 (3 y)
Stauder et al (2012)[34]	IC: 26	IC: 49	IC: 18	NR	IC: 2.2	IC: 36.1	96/80 (1 y) 69/66 (3 y)	2/8	15/NR (1 y) 28/27 (3 y)
Kano et al (2010)[10]	IC: 21	IC: 32	IC: 15	NR	IC: 2.2	IC: 27.6	85/78 (1 y) 23/42 (3 y)	2/10	28/NR (FU) NR/33.6 (1 y) NR/80.3 (3 y)
Liu et al (2009)[29]	IC: 6	IC: 6	IC: 24	NR	NR	IC: 28	100/100	3/50	0/0
Merchant et al (2008)[14]	IC: 6	IC: 6	IC: 18	NR	NR	IC: 18.5	20/NR (5 y) NR/18.5 (mo)	1/16.7	66.7/33.3 (last FU)
Combs et al (2006)[38]	IC: 19	IC: 19	IC: 36	IC: 5	IC: 17.8	IC: 32	77/60 (5 y) NR/64 (10 y)	0	26.3/31.6
Lo et al (2006)[6]	IC: 8	IC: 13	IC: 14	IC: 1	IC: 1	IC: 30.2	75/62.5 (1 y) NR/50 (3 y)	2/25	26.8/13.5 (1 y) 39/27.1 (3 y)
Endo et al (2004)[35]	IC: 2	IC: 11	IC: 22	NR	NR	IC: 85.5	100/100	0/0	NR
Mansur et al (2004)[36]	IC: 9	IC: 9	IC: 16	NR	IC: 5.4	IC: 28	71.1/55.6 (3 y)	2/2	NR
Benzil et al (2004)[37]	SP: 1	NR	NR	NR	NR	SP: 12	Pat. died at 12 mo/6 (mo)	1/100	6/6 (mo)
Ryu et al (2003)[16]	SP: 2	NR	SP: 18	NR	NR	SP: 6.5	100/100	0	0/0
Hodgson et al (2001)[17]	IC: 28	NR	IC: 4.5	24	NR	NR	NR/8.5 (mo) NR/22 (3 y)	NR	71/NR (3 y)
Stafford et al (2000)[41]	IC: 12	IC: 17	IC: 18	NR	IC: 3.2	IC: 22.5	40/18 (mo)	2/17	32/16.7 (3 y)
Jawahar et al (1999)[18]	IC: 22	IC: 22	IC: 16.1	1	IC: 13.7	IC: 21	26.4/NR (mo) NR/32 (3 y)	1/4.5	37.7/36.3 (3 y)
Aggarwal et al (1997)[8]	IC: 5	IC: 5	IC: 10	NR	NR	IC: 24	80/80 (last FU)	1/20	20/0
Weprin et al (1996)[20]	IC: 3	IC: 3	IC: 20	NR	IC: 7.54	IC: 17	33/33.3	1/33.3	33.3/0
Grabb et al (1996)[21]	IC: 7	IC: 7	NR	NR	NR	IC: 6	14.3/14.3 (5 y)	NR	42.9/57.1
Hirato et al (1995)[22]	IC: 3	IC: 4	NR	1	NR	NR	NR/75	NR	25/0
Loeffler et al (1990)[23]	IC: 2	NR	NR	NR	NR	IC: 9	100/100	NR	0/0

ARE, adverse radiation effect; fr, fractionated; FU, follow-up; IC, intracranial; No., number; NR, not reported; OS, overall survival; PFS, progression-free survival; SP, spinal; unfr, unfractionated.

Symptomatic outcomes are pivotal in ependymoma treatment, directly affecting patients' quality of life.[40] Our study suggests a higher rate of symptom improvement compared to previous literature.[28] Interestingly, no significant difference was observed in the percentage of patients experiencing symptom improvement between adults and children. However, patients with grade 2 ependymomas exhibited a higher rate of symptomatic improvement (65.2%) compared with grade 3 tumors (34.8%). These findings indicate that SRS effectively alleviates symptoms, particularly in patients with lower-grade tumors, with its effectiveness seemingly less influenced by age. Nevertheless, long-term follow-up remains crucial to assess the sustainability of these improvements and to identify potential late-onset complications.[39]

WHO Grades and Their Impact on Patient Outcomes

The WHO classification remains an invaluable prognostic tool in ependymoma management.[24] Patients with grade 2 ependymomas demonstrated an outstanding 5-year OS rate of 100%, contrasting with those with grade 3 tumors (35.9%, $P < .001$). These findings underscore the significance of precise grading and tailored treatment approaches. Furthermore, our analysis unveiled a notable tendency for grade 2 ependymomas progressing to grade 3 during follow-up, emphasizing the dynamic nature of tumor progression and the importance of vigilant monitoring, particularly in pediatric cases.[42]

The aggressive nature of intracranial ependymomas in pediatric patients presents challenges in responding to conventional therapies, including SRS. The dynamic neurodevelopmental milieu of the pediatric brain introduces complexities in SRS treatment because of ongoing neuronal maturation and the presence of susceptible neural progenitor cells. Enhanced exposure of adjacent healthy brain tissue to radiation, compounded by the immaturity of the blood-brain barrier, accentuates the predisposition toward enduring adverse effects, including radiation-induced necrosis and cognitive impairment.[43]

Regular and frequent follow-up is paramount for grade 3 ependymoma patients, enabling early detection of tumor recurrence or progression.[1] Shared decision-making and informed consent play critical roles in treatment.[28] Patients and their families must receive comprehensive information regarding treatment options, potential risks, and benefits associated with SRS. A multidisciplinary approach involving neurosurgeons, radiation oncologists, and pediatric oncologists is indispensable for devising personalized treatment plans.[44]

Age Stratification and Tumor Distribution

Stratifying our cohort by age revealed a notable pattern: grade 2 ependymomas were predominantly observed in adults (84.1%), whereas grade 3 tumors were more prevalent among pediatric patients (71%). This age-related distribution underscores inherent variances in tumor biology, necessitating tailored diagnostic and treatment strategies for each age group. The higher prevalence of grade 3 ependymomas in pediatric patients underscores the aggressive nature of these tumors in younger populations, warranting vigilant surveillance and aggressive therapeutic interventions, including modalities with higher doses tailored for pediatric patients.

Several factors may contribute to this age distribution. First, it could reflect the survival bias, wherein adult patients previously diagnosed with ependymoma during childhood have survived into adulthood, potentially leading to an underrepresentation of aggressive cases in the adult cohort. Our study, spanning from 1998 to 2023, with longer median follow-up duration in adults (42.7 months) compared with pediatric patients (37 months), suggests that adult patients may include individuals diagnosed earlier in childhood who have undergone prolonged treatment and follow-up assessments within our institution as adults. Consequently, this prolonged survival may contribute to a seemingly lower proportion of aggressive grade 3 tumors among adult patients.

Importantly, our study identifies a positive correlation between initiating treatment at a younger age and both OS and PFS, suggesting potential benefits of early intervention. In addition, prolonged follow-up periods were associated with enhanced OS.

Adverse Radiation Effects

Our investigation reveals a significant increase in ARE among pediatric patients (21.4%), surpassing previously reported rates.[28] This highlights the critical importance of meticulous patient selection and precise treatment planning when employing SRS.[10] The elevated incidence of radiation necrosis and associated toxicities in this demographic emphasizes the inherent risks of SRS in pediatric populations. A comprehensive assessment of patient-specific factors, including age, prior radiation exposure, and tumor volume, is indispensable to mitigating the risk of ARE. For individuals at higher risk, alternative treatment modalities such as chemotherapy or conventional radiotherapy should be carefully considered.[45]

Limitations

The retrospective nature of our study may introduce biases, cautioning against direct comparisons between SRS and surgery, and interpretation of prognostic factors. Prolonged follow-up is crucial for thorough evaluation of SRS safety and efficacy. Larger sample sizes are imperative to validate associations, such as the link between lower SFED and enhanced LTC. The rarity of ependymoma complicates subgroup analyses, and distinguishing between local recurrence and ARE requires extended monitoring.

CONCLUSION

In conclusion, our study stands as the largest long-term experience using CyberKnife SRS for treating WHO grade 2 and 3 intracranial and spinal ependymomas across pediatric and adult populations at a single institution. These findings affirm SRS as a

viable and effective therapeutic option for ependymoma management. To optimize treatment outcomes and minimize adverse events, especially in pediatric cases, judicious patient selection, tailored treatment planning, and diligent long-term follow-up are essential. Our study provides valuable insights for clinicians and researchers, underscoring the ongoing imperative to explore and refine SRS approaches for central nervous system ependymomas.

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COMMENTS

Primary ependymoma is a relatively rare central nervous system tumor for which the gold standard treatment remains gross total surgical resection followed by radiation, with chemotherapy added in refractory cases.[1a] Ependymoma in children are more frequently encountered intracranially and are more likely to be diagnosed at grade 3; whereas adult ependymomas are typically found in the spine and are more frequently grade 2.[2a,3a] Higher grade lesions are associated with shorter progression-free intervals and less favorable response to standard treatments. Recurrent ependymoma presents a greater clinical challenge, with greater morbidity, and there is no firm consensus on optimal treatment at time of recurrence.[4a]

In this study, the authors retrospectively review all patients in their institution who underwent stereotactic radiosurgery (SRS) for any ependymoma (new or recurrent). Pediatric and adult patients were analyzed as two separate groups for all factors. Overall favorable response of ependymoma to SRS was high—78% of treated tumors had good 5-year local tumor control, 67% of patients reporting symptomatic improvement, and only 7% experiencing AREs. These data point toward the general safety and efficacy of SRS as a treatment modality for ependymoma.

In this era of molecular characterization and targeted treatments, nuanced analysis allows for more precise therapeutic attack. The authors reported that pediatric patients were more likely to have grade 3 ependymoma (75% of pediatric tumors vs 16% of adult tumors) as well as poorer outcome; however, tumor grade was not analyzed independent of patient age in terms of outcome or response to SRS, nor were recurrent tumors (which frequently gain additional or novel mutations affecting response to radiation) analyzed separately from primary lesions. It is noted that the rarity of this entity hinders data collection and powered analysis and that the authors present the largest institutional series to date. Future studies examining the efficacy of SRS by molecular or histologic subtypes would enable clinicians to select the most effective treatment for each lesion regardless of age or recurrence. Collection of multi-institutional data sets with larger patient numbers and increased follow-up will allow for studies with more power and assessment of long-term outcomes.

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The presented study is a retrospective analysis on 34 patients with 75 ependymomas following CyberKnife SRS between 1998 and 2023 at a single institution of both pediatric and adult patients to determine the efficacy and safety of SRS for grade 2 and 3 ependymomas. They found that SRS is a viable modality for these lesions but that SRS had lower local tumor control and was less effective in grade 3 cases. The strengths of this study are reasonably consistent methodology and SRS utilized at a single institution and ability to collect follow-up data across what is likely to be multiple record systems. The weakness of the study includes the study period length (ie, 25 years) and likely changes in provider/SRS techniques and advances, likely differences in surgeon and surgical technique, patients with limited follow-up (eg, only 3 months in some cases) that limits the scope information on longer term outcomes, and disparate age-groups in a disease where age has a significant impact on prognosis. Additionally, the inclusion of patients without pathologically proven tumor has the potential to skew results as it is not certain what the tumor type and grade is without tissue. This study highlights the potential benefits of SRS approaches for CNS ependymomas and that this modality should be considered as an option in the therapy of these following surgical resection and in the recurrent disease state. Because of the many limitations noted, this report is not useful as formal guidance in the management of this disease. The study does bring to light what is necessary to move knowledge on this topic forward. To accomplish that, future studies at the reporting institution or others should await longer follow-up periods and stratification by lesion size, location, and subject age to effectively determine the efficacy of SRS for CNS ependymomas.

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