

Pediatric cranial stereotactic radiosurgery: Meta-analysis and international stereotactic radiosurgery society practice guidelines

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Abstract

Background. There are limited data on the use of stereotactic radiosurgery (SRS) for pediatric patients. The aim of this systematic review was to summarize indications and outcomes specific to pediatric cranial SRS to inform consensus guidelines on behalf of the International Stereotactic Radiosurgery Society.

Methods. A systematic review, using the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses, analyzed English-language articles on SRS, published between 1989 and 2021, that included outcomes for at least 5 pediatric patients. MEDLINE database terms included tumor types and locations, and radiosurgical and age-specific terms. We excluded nonclinical reports, expert opinions, commentaries, and review articles. Meta-regressions for associations with local control were performed for medulloblastoma, craniopharyngioma, ependymoma, glioma, and arteriovenous malformation (AVM).

Results. Of the 113 articles identified for review, 68 met the inclusion criteria. These articles described approximately 400 pediatric patients with benign and malignant brain tumors and 5119 with AVMs who underwent cranial SRS. The rates of local control for benign tumors, malignant tumors, and AVMs were 89% (95% CI, 82%–95%), 71% (95% CI, 59%–82%), and 65% (95% CI, 60%–69%), respectively. No significant associations were identified for local control with the patient-, tumor-, or treatment-related variables.

Conclusions. This review is the first to summarize outcomes specific to SRS for pediatric brain tumors and AVMs. Although data reporting is limited for pediatric patients, SRS appears to provide acceptable rates of local control. We present ISRS consensus guidelines to inform the judicious use of cranial SRS for pediatric patients.

Key Points

- Cranial stereotactic radiosurgery (SRS) for pediatric brain tumors and arteriovenous malformations yields durable local control and obliteration, respectively.
- This analysis found no patient, tumor, or treatment factors associated with local control.
- SRS toxicity rates are related to prior therapy.

Because pediatric patients are still growing and developing, they are more sensitive to the late effects of radiotherapy.¹ Pediatric cranial radiation therapy can impact neurocognition,^{1,2} hearing,^{3,4} growth,⁵ and neuroendocrine and neurovascular outcomes,⁶ and it can increase the risk

of secondary malignancy.^{1,2} Efforts to reduce these adverse effects include smaller target volumes and advanced techniques such as intensity-modulated radiotherapy^{7–9} and proton therapy^{4,10–12}; these methods are now widely used for upfront management of pediatric brain tumors. Stereotactic

Importance of the Study

This systematic review gathers data on pediatric stereotactic radiosurgery for benign and malignant cranial tumors and arteriovenous malformations (AVMs), an area for which there is a paucity of evidence-based recommendations. The studies in this review demonstrate that durable local control is possible for benign and malignant pediatric cranial tumors and that the obliteration rates for AVM are similar to those of adults. The rates

and severities of toxicity varied widely among studies. Patient, tumor, and treatment prognostic variables were assessed for potential association with local control; there were no significant associations. Gathering these data allowed the authors to present an overview of the utility and outcomes of pediatric cranial radiosurgery to inform the development of consensus guidelines.

radiosurgery (SRS) also has the potential to reduce the late effects associated with pediatric cranial radiotherapy given its superior dose conformality.

SRS is defined by the use of multiple intersecting beams of highly focused ionizing radiation, delivered over 1–5 sessions, to a stereotactically localized target volume. Rapid dose fall-off is inherent to the SRS dose distribution, which minimizes the dose to the surrounding normal structures. As a result, this highly focused and locally ablative tool can minimize late effects for younger patients.^{1,13} Benefits also include a smaller impact on daily quality of life and education, quicker recovery, and less anesthesia exposure.^{2,14} Although there is an abundance of data on SRS in adults,^{15–18} data are limited for pediatric patients.

The purpose of this systematic review is to summarize the patient, tumor, and treatment characteristics, indications, and outcomes for pediatric patients undergoing cranial SRS. Based on the results of this review, the authors have developed consensus guidelines for the judicious use of SRS in pediatric patients on behalf of the International Stereotactic Radiosurgery Society (ISRS).

Methods

Evidence Acquisition

This review followed the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) to ensure proper methodology.¹⁹ Ethical approval was not required. The screening, inclusion, and exclusion process is shown in [Supplementary Figure 1](#). A comprehensive search was conducted in the MEDLINE database for all articles published between 1989 and 2021. The database was last searched on April 1, 2022. Search terms included diagnoses (eg, ependymoma, medulloblastoma, low-grade glioma, high-grade glioma, pilocytic astrocytoma, glioblastoma, arteriovenous malformation [AVM], craniopharyngioma, and metastasis), tumor locations, radiosurgical terms, and the age-specific terms “pediatric,” “adolescent,” “children,” “childhood,” and “young adults.” Database searches were supplemented by manual searching of manuscript references. The inclusion criteria were English-language publication, reporting of outcomes, and inclusion of at least 5 pediatric patients who underwent 1–5 sessions of SRS for a malignant or benign brain tumor or AVM. Studies were excluded

if they had fewer than 5 eligible patients or consisted of nonclinical reports, expert opinion, commentary, or review articles. When multiple publications of the same clinical cohort were found, only the most recent study was included.

Data Extraction

One author (E.S.M.) conducted a thorough assessment of all potentially relevant manuscripts to identify studies that fulfilled the inclusion criteria. Data collection was performed on standardized extraction forms in which baseline clinical, radiotherapy-specific, and outcomes data were extracted. Data from independent studies were cross-checked by 3 reviewers (E.S.M., S.S., and J.Q.). The following information was extracted from each included study: first author, publication year, sample size, percentage of female patients, average patient age, percentage of patients who had prior surgery, percentage of patients who had prior radiation therapy, average SRS dose (Gy), average follow-up (months), average tumor volume (cm³), type of tumor, percentage of patients achieving local control (LC), and time at which LC was assessed.

Median values were used for average age and follow-up duration. When median values were not available, mean values were used. In studies where neither the median age nor mean age was available, the minimum and maximum age were used to determine the average age.

Average age:

$$\frac{\text{minimum age} + \text{maximum age}}{2}$$

Mean values were used for the average SRS dose and tumor size. When mean dose values were not available, median values were used. In the absence of a mean and median dose, the minimum and maximum doses were used to determine the average dose.

Average dose:

$$\frac{\text{minimum dose} + \text{maximum dose}}{2}$$

If mean, minimum, and maximum tumor-size data were not available but a median tumor size was available, the median was used as the average tumor size. If a study reported results for multiple-fraction SRS, the median single-fraction dose was used for analysis. When mean tumor size

Table 1. Medulloblastoma

First Author	Year	No. of Patients	Female Sex, %	Average Age, y	Average Tumor Size, cm ³	Prior Surgery, %	Prior RT, %	Average Dose, Gy	Average Follow-up, mo	Local Control, % (SE)	Time Local Control Assessed
Flannery ²³	2009	7	57.14	2.70 ^a	6.3 ^b	100.00	85.71	14.5 ^a	NR	71 (17.15)	NR
Napieralska ²⁴	2019	14 ^c	57.14	22.00 ^a	NR	85.71	100.00	14.5 ^b	14.3 ^a	75.00 (11.57)	NR

Abbreviations: NR, not reported; RT, radiotherapy.

^aReported as the median.

^bReported as the mean.

^cIncluded patients with medulloblastoma and ependymoma.

data were not available but median, minimum, and maximum tumor-size data were available, the following formula was used to calculate the average tumor size²⁰:

Average tumor size:

$$\frac{\text{minimum tumor size} + \text{maximum tumor size} + (2 \times \text{median tumor size})}{4}$$

The primary outcome of interest was LC at ≤5 years. Studies that did not have the timeline or duration of LC specified (undated or not reported) were assumed to be less than 5 years and were included in the analyses. Studies that did not report LC but did provide progression-free survival (PFS) ≤5 years were included in the analysis, and PFS was used as a surrogate for LC. The rates of LC and 95% confidence intervals (CIs) were tabulated as forest plots.

For each category of pediatric diagnosis, a total of 7 meta-regressions were performed. The rate of LC was assessed against average patient age, patient sex, average tumor size, prior surgery, prior radiotherapy, average SRS dose, and average follow-up duration. These same meta-regressions were also performed for benign tumors (craniopharyngioma and low-grade glioma) and malignant tumors (ependymoma, medulloblastoma, and high-grade glioma).

Data and Statistical Analysis

All data analyses were performed using Stata software, version 14.2 (StataCorp LLC) using the Metaprop, Metabias, and Metafunnel packages with a 2-tailed alpha level of 0.05 considered statistically significant. Weighted random effects models were used to calculate pooled estimates for LC because they incorporate both within- and between-study components of variance.²¹ Additional subgroup analysis was performed by grouping studies into different disease categories.

The level of heterogeneity between studies was measured using the Cochran *Q* test and the *I*² statistic. A Cochran *Q* value <0.1 indicated significant heterogeneity. The *I*² statistic was used to classify heterogeneity as low (≤50%), moderate (51%–75%), or high (≥76%)²² Visual inspection of funnel plots and the Egger test (*P* < .05 indicating presence of bias) were used to identify publication bias. Finally, meta-regression was used to determine any relationship between prognostic factors (age, sex, average dose, average

follow-up duration, prior radiotherapy, and prior surgery) and LC.

The required programming and analyses were performed by 1 author (M.A.A.). The final code was reviewed independently by 1 author (A.S.) for quality assurance.

Results

A total of 113 articles were identified for review; 68 were included in the final analysis. All analyzed studies were published between 1989 and 2021; 3 included patients up to age 25 in the “pediatric” age group, and 9 included adult patients beyond 25 years of age in their analyses.

Medulloblastoma

Table 1 summarizes the results of all studies assessing SRS for pediatric medulloblastoma (recurrent or metastatic). The data were extremely limited for this cancer type: only 2 studies were available, and one of these included patients with ependymoma.^{23,24} In these 2 studies, 57% of patients were female, and there were 11 pediatric patients (≤18 years of age); the average median age was 12.35 years (including adult patients). Average tumor volume was only reported in 1 study (mean, 6.3 cm³).²³ Patients received an average SRS dose of 14.5 Gy, and most had undergone prior surgery or radiotherapy. The average rate of LC was 73% (95% CI, 67%–79%). The time that LC was assessed was not reported by either study, and the median follow-up duration was only reported by 1 study.^{23,24}

It was not possible to perform any meta-regressions for pediatric medulloblastomas because of insufficient observations.

Craniopharyngioma

Table 2 summarizes the reported results of SRS for pediatric craniopharyngioma. There were 6 studies available for analysis.^{1,5,25–28} Three of these included adults: in 1 study, patients ranged from 3 to 85 years of age,²⁶ in another they ranged from 3 to 44 years of age,⁵ and in the third, only 15 of the 49 patients were under 15 years of age.²⁷ Across all studies, 57.2% of patients were female (range, 51.2%–63.2%), with an

Table 2. Craniopharyngioma

First Author	Year	No. of Patients	Female Sex, %	Average Age, y	Average Tumor Size, cm ³	Prior Surgery, %	Prior RT, %	Average Dose, Gy	Average Follow-up, mo	Local Control, % (SE)	Time Local Control Assessed
Albright ²⁵	2005	5	NR	13 ^a	0.65 ^a	85.7	NR	NR	29 ^b	NR	–
Amendola ⁵	2003	14	57.1	11.5 ^a	3.7 ^b	NR	14.28	14.4 ^b	39.2 ^b	86 (9.27)	5 y
Eder ¹	2001	7	NR	11 ^b	NR	NR	7.93	10.4 ^b	NR	86 (13.11)	3 y
Iwata ²⁶	2012	43	51.2	44 ^a	2 ^a	89.4	0	14.3 ^a in 1 fraction; 21 ^a in 3 fractions	40 ^a	85 (5.45)	3 y
Martínez-Moreno ²⁷	2013	49	NR	32 ^b	NR	57.14	12.24	NR	45 ^b	97 (2.44)	5 y
Pérez Bovet ²⁸	2012	19	63.2	13 ^a	NR	89.4	5.2	13.4 ^b	51.5 ^a	NR	–

Abbreviations: NR, not reported; RT, radiotherapy.

^aReported as the median.

^bReported as the mean.

Table 3. Ependymoma

First Author	Year	No. of Patients	Female Sex, %	Average Age, y	Average Tumor Size, cm ³	Prior Surgery, %	Prior RT, %	Average Dose, Gy	Average Follow-up, mo	Local Control, % (SE)	Time Local Control Assessed
Aggarwal ²⁹	1997	5	80.00	2.00 ^a	NR	NR	100	11.25 ^b	24 ^a	80.00 (17.89)	5 y
Hoffman ³⁰	2014	12	NR	NR	NR	100	100	24 ^a	25 ^a	89 (9.03)	2 y
Kano ³¹	2019	89	NR	16.3 ^a	2.2 ^a	100	100	15 ^a	NR	48 (5.30)	5 y (PFS)
Kawamura ³²	2016	21	NR	NR	NR	100	100	NR	123.4 ^a	NR	–
Lo ³³	2006	8	75.00	11.30 ^a	1 ^a	NR	87.5	14 ^a	30.2 ^a	77.00 (14.88)	5 y
Merchant ³⁴	2008	6	NR	NR	NR	100	100	18 ^a	NR	NR	–

Abbreviations: NR, not reported; PFS, progression-free survival; RT, radiotherapy.

^aReported as the median.

^bCalculated average.

average age of 20.75 years (range of averages, 11–44 years). The average tumor volume was 2.12 cm³ (range of averages, 0.65–3.7 cm³). The average SRS dose was 13.13 Gy (range of averages, 10.4–14.4 Gy), 7.93% of patients had undergone prior radiotherapy (range, 0%–14.28%), and 80.5% of patients had undergone prior surgery (range, 57.14%–89.4%). The average follow-up period was 40.94 months (range of averages, 29–51.5 months). The average rate of LC was 89% (95% CI, 82%–95%).^{5,26,27}

Meta-regression for LC showed no significant association with average patient age ($P = .929$), prior radiotherapy ($P = .383$), average SRS dose ($P = .968$), or average follow-up duration ($P = .271$). It was not possible to perform meta-regressions for LC against patient sex, average tumor size, or prior surgery because of insufficient observations.

Ependymoma

Table 3 summarizes the results of studies assessing SRS for pediatric ependymoma (as upfront therapy or for

recurrence). Six studies were available for analysis.^{29–34} In these studies, 77.5% of the patients were female (range, 75%–80%; percentage not reported in 4 studies), and the average median age was 9.87 years (range of medians, 2.0–16.3 years). The average median tumor volume was 1.6 cm³ (range of medians, 1.0–2.2 cm³), and 97.9% of patients had received prior radiotherapy (range, 87.5%–100%). The average SRS dose was 16.45 Gy (range of averages, 11.25–24 Gy), and the average median follow-up period was 50.65 months (range of medians, 24–123.4 months). Reported rates of LC ranged from 48% to 89%^{29,30,33}; the average rate of LC was 75% (95% CI, 56%–89%).

Meta-regression for LC showed no significant association with average age ($P = .312$), prior radiotherapy ($P = .849$), average SRS dose ($P = .565$), or follow-up duration ($P = .692$). It should be noted that the average tumor volume did not vary widely (1.0–2.2 cm³). It was not possible to perform meta-regressions for LC against prior surgery because of collinearity (all reported prior surgery values were 100%) or for LC against patient sex or tumor size because of insufficient observations.

Table 4. Glioma

First Author	Year	No. of Patients	Female Sex, %	Average Age, y	Average Tumor Size, cm ³	Prior Surgery, %	Prior RT, %	Average Dose, Gy	Average Follow-up, mo	Local Control, % (SE)	Time Local Control Assessed
Boëthius (low grade) ³⁵	2002	19	36.84	7 ^a	3.3 ^b	89.47	NR	11.3 ^b	70.8 ^b	100	–
Eder (low grade) ¹	2001	12	NR	13 ^b	4.2 ^b	76.92	22.22	14.9 ^b	38.2 ^b	78 (11.96)	NR
Kano (low grade) ³⁶	2009	50	44	10.5 ^a	2.9 ^b	82	15.79	14.5 ^a	55.5 ^a	94.74 (3.16)	5 y
Seblani (low grade) ³⁷	2016	9	NR	11.2 ^b	NR	NR	NR	11.5 ^b	NR	77.8 (16.65)	NR
Somaza (low grade) ³⁸	1996	9	NR	NR	4.2 ^b	77.78	NR	15 ^b	19 ^b	100 (0.00)	5 y
Weintraub (low grade) ³⁹	2012	24	45.83	11 ^a	2.4 ^b	83	12.50	15.0 ^a	144 ^a	83.33 (7.61)	5 y
Eder (high grade) ¹	2001	12	NR	7.0	2.7 ^b	100	100	18.8 ^b	32 ^b	50 (14.43)	NR
Hankinson (high grade) ⁴⁰	2014	7	NR	4.5 ^a	NR	NR	NR	25 ^a	NR	NR	–

Abbreviations: NR, not reported; RT, radiotherapy.

^aReported as the median.

^bReported as the mean.

Glioma

Table 4 summarizes the results of the 7 available studies on SRS for pediatric glioma; 5 reported results for low-grade glioma, 1 for high-grade glioma, and 1 reported result for both.^{1,35–40} In these studies, 42.2% of patients were female (range, 36.84%–45.83%; percentage not reported in 5 studies), and the average age was 9.17 years (range of averages, 4.5–13 years). The average tumor volume was 3.28 cm³ (range of averages, 2.4–4.2 cm³). Most patients (84.86%) had undergone prior surgery (range, 76.92%–100%), and 37.63% had undergone prior radiotherapy (range, 12.5%–100%). The average SRS dose was 15.75 Gy (range, 11.3–25 Gy), and the average follow-up period was 59.92 months (range, 19–144 months). Rates of LC ranged from 50% to 100%; the average rate of LC was 84% (95% CI, 71%–94%).

Meta-regression for LC showed no significant association with an average age ($P = .227$), average tumor size ($P = .707$), prior radiotherapy ($P = .789$), average SRS dose ($P = .716$), or average follow-up duration ($P = .782$). It was not possible to perform meta-regressions for LC against patient sex or prior surgery because of insufficient observations. We did not analyze gliomas by grade in this portion of the analysis because only 2 studies included high-grade gliomas, and one of those did not report LC.

Arteriovenous Malformation

By far the most extensive data were available for pediatric AVM (Table 5). Forty-nine articles that included pediatric patients were reviewed for this analysis.^{1,14,41–87} Most

articles focused exclusively on pediatric patients; however, Chen et al (2018) included an equal number of pediatric and adult patients to compare the 2 cohorts,⁴⁶ and Daou et al had only 42 pediatric AVMs in the 160 included lesions (in 148 patients).⁵¹ Across all studies, 48.33% of patients were female (range, 33.01%–71.4%), and the average age was 13.4 years (range of averages, 9.5–16 years). The average tumor size was 4.99 cm³ (range of averages, 0.6–33 cm³), 23.66% of patients had undergone prior surgery and/or embolization (range, 0%–50%), and 5.76% had undergone prior radiotherapy (range, 0%–37.5%). The average follow-up duration was 61.52 months (range of averages, 21–136 months). Rates of LC (obliteration) ranged from 19% to 94.7%.

Figure 1 provides a forest plot showing the cumulative rate of LC for all AVM studies: 65% (95% CI, 60%–69%). Meta-regression for LC showed no significant association with female sex ($P = .351$), average age ($P = .305$), average tumor size ($P = .426$), prior surgery ($P = .912$), prior radiotherapy ($P = .163$), average SRS dose ($P = .075$), or average follow-up duration ($P = .525$).

The average mean value for the SRS dose was 20.39 Gy (range, 15–28 Gy). Studies showing a rate of LC $\geq 65\%$ had average SRS doses of 21.06 Gy (range, 16.9–28 Gy).^{1,14,41–43,51,53,55,57,59–61,63,64,67,68,70,75,77,79–81,85–87}

Benign Tumors

When all benign tumor types were grouped together (including craniopharyngioma and pilocytic astrocytoma but excluding AVM), 49.7% of patients were female, and the

Table 5. Arteriovenous Malformation

First Author	Year	No. of Patients	Female Sex, %	Average Age, y	Average Lesion Size, cm ³	Prior Surgery, %	Prior RT, %	Average Dose, Gy	Average Follow-up, mo	Obliteration Rate, % (SE)	Time Local Control Assessed
Barton ⁴¹	2016	24	NR	12.1 ^a	NR	NR	NR	NR	34.8 ^a	71 (9.26)	5 y
Blamek ⁴²	2013	10	60.00	16 ^a	13.2 ^b	10	NR	19 ^b	38.5 ^a	80 (12.65)	5 y
Börcek ⁴³	2014	75	58.60	12.00 ^a	3.5 ^a	9.6	0	20.8 ^b	32 ^a	68.9 (5.35)	5 y
Burke ⁴⁴	2020	345	47.3	12.8 ^b	4.3 ^b	16.2 ^c	15.4	20.8 ^b	91.1 ^b	64 (2.58)	NR
Capitanio ⁴⁵	2019	33	51.5	15 ^a	3.6 ^a	30.4 ^d	0	21.4 ^b	65 ^a	60.6 (8.51)	NR
Chen ⁴⁶	2018	315	46.2	12.4 ^a	3.5 ^a	26.9 ^c	13.3	21 ^b	92.3 ^b	64.2 (1.05)	5 y
Chen (ruptured) ⁴⁷	2019	386	50.8	12.7 ^b	4.4 ^b	21.5 ^c	13.2	20.4 ^b	87.7 ^b	61 (2.48)	4 y
Chen (unruptured) ⁴⁷	2019	153	38.6	13.3 ^b	9.6 ^b	26.8 ^c	11.8	19.4 ^b	81.2 ^b	51.2 (4.00)	4 y
Chen ⁴⁸	2020	101	38.60	13.50 ^b	9 ^b	0	0	19.2 ^b	80.8 ^b	64 (4.78)	5 y
Chen ⁴⁹	2020	539	47.30	13.3 ^a	5.9 ^b	16.9 ^e	12.8	20.2 ^b	68.6 ^a	63.6 (2.07)	5 y
Cohen-Gadol ⁵⁰	2006	38	63.16	15 ^a	3.4 ^a	2.63	2.63	20 ^a	42 ^a	54 (8.09)	Immediate
Daou ⁵¹	2021	148	47.5	35.6 ^b	7.4 ^b	NR	NR	16.5 ^a	56.5 ^a	77.0 (3.5)	–
Demir ⁵²	2016	194	NR	13.00 ^a	3.2 ^a	NR	NR	23 ^a	54 ^a	37.6 (3.48)	5 y
Dinca ⁵³	2012	363	NR	12 ^b	3.75 ^b	16 ^c	NR	22.7 ^b	NR	82.7 (1.99)	5 y
Ding ⁵⁴	2015	51	47.10	13.3 ^a	3.2 ^a	27.5 ^e	NR	21.3 ^b	45 ^a	54 (6.98)	5 y
Eder ¹	2001	10	NR	12 ^b	5 ^b	30 ^e	NR	21 ^b	50.4	80 (12.65)	Various
Fuss ⁵⁵	2005	7	71.40	13 ^a	13.8 ^a	14.2 ^e	0	18.2 ^b	32 ^a	71.4 (17.08)	22 mo
Glazener ⁵⁶	2020	34	44.1	14.4 ^a	2.91 ^a	11.8	0	16.8 ^a	98 ^a	64.7 (8.2)	5 y
Hanakita ⁵⁷	2015	116	55.17	14.00 ^a	1.8 ^a	20.69	0	20 ^a	100 ^a	88 (3.02)	5 y
Hasegawa ⁵⁸	2019	189	40.74	11.00 ^a	2.2 ^a	36.75 ^c	0.053	20 ^a	136 ^b	64 (3.49)	5 y
Kano ⁵⁹	2012	135	44	12 ^a	2.5 ^a	34.8 ^c	NR	20 ^a	71.3 ^a	67 (4.05)	5 y
Kasliwal ⁶⁰	2009	156	NR	13 ^b	3 ^b	NR	NR	24.3 ^a	NR	85 (2.86)	4 y
Kiran ⁶¹	2007	103	33.01	13.9 ^b	1.2 ^a 2.4 ^b	7.77	NR	24.4 ^b	26.4 ^b	86 (3.42)	4 y
Kondziolka ¹⁴	1990	39	48.72	12.2 ^b	NR	NR	NR	21.9 ^b	36.2 ^b	75 (6.93)	NR
Lee ⁶²	2021	24	NR	14 ^a	8.14 ^a	48.0 ^c	NR	22.5	54 ^a	48 (10.2)	5 y
Levy ⁶³	1989	40	37.5	14 ^a	7.05 ^a	37.5 ^c	0	28 ^a	NR	77.8 (6.57)	2 y
Levy ⁶⁴	2000	53	NR	12 ^a	1.7 ^a	32.08 ^f	NR	20 ^a	NR	73.58 (6.06)	NR
Maity ⁶⁵	2004	17	52.94	12 ^a	6.9 ^a	41.18 ^c	0	18 ^a	21 ^a	53 (12.10)	3 y
Nata ⁶⁶	2003	49	57.14	12 ^a	3.5 ^a	26.6 ^g	NR	23.8 ^b	34 ^a	61.2 (6.96)	>3.5 y
Nicolato ⁶⁷	2015	100	54	12.8 ^b	2.8 ^b	38 ^c	5 ^h	20.2 ^b	82.2 ^a	76 (4.27)	5 y
Par ⁶⁸	2008	105	47.62	10 ⁱ	33 ⁱ	NR	NR	20 ^{b,i}	25 ^a	81 ^j (3.83)	NR
Park ⁶⁹	2017	68	48.53	13.3 ^b	2.1 ^a	25 ^c	0	22.9 ^b	61.9 ^b	38.2 (5.89)	5 y
Pašalić ⁷⁰	2018	28	37	14	3.5 ^b	9.1	NR	22.4 ^b	NR	77.3 (7.92)	5 y
Patibandla ⁷¹	2017	28	46.4	12.1 ^b	5.9 ^b	24.9 ^c	10.7	19.4 ^b	116 ^b	19 (7.41)	5 y
Pollock ⁷²	2010	48	58.33	NR	3.5 ^a	NR	NR	18 ^a	73.5 ^a	63 (6.97)	5 y
Potts ⁷³	2014	80	39	12.7 ^b	3.1 ^a	10	37.5	17.5 ^a	46 ^a	34 (5.3)	5 y

Table 5. Continued

First Author	Year	No. of Patients	Female Sex, %	Average Age, y	Average Lesion Size, cm ³	Prior Surgery, %	Prior RT, %	Average Dose, Gy	Average Follow-up, mo	Obliteration Rate, % (SE)	Time Local Control Assessed
Rajshekhar ⁷⁴	2016	69	47.83	14 ^a	8.5 ^b	18.84 ^c	NR	15 ^a	22 ^a	63.8 (5.79)	22 mo
Reyns ⁷⁵	2007	100	44	12 ^a	2.8 ^b	50 ^c	NR	23 ^b	NR	70 (4.58)	5 y
Sheth ⁷⁶	2014	42	43	12 ^b	4.6 ^a	26 ^c	0	18.3 ^a	NR	30 (7.07)	3 y
Shin ⁷⁷	2002	100	58	14 ^a	1.8 ^a	32 ^k	0	20 ^a	71 ^a	94.7 (2.24)	5 y
Smyth ⁷⁸	2002	31	35.48	11.2 ^a	1.6 ^a 5.37 ^b	29 ^c	6.5	18 ^a 16.7 ^b	60 ^a	35 (8.57)	5 y
Starke ⁷⁹	2017	357	45.7	12.6 ^b	3.5 ^b	28.2 ^c	13.2	21 ^b	92.4 ^b	70.2 (2.42)	5 y
Tamura ⁸⁰	2012	22	36.36	9.5 ^a	1.2 ^a	18.2 ^l	0	22 ^a	60.5 ^b	77.00 (8.97)	5 y
Umansky ⁸¹	2018	14 ^m	50	15.3 ^b	0.6 ^a	NR	NR	21.49 ^a	49.9 ^a	71 (12.13)	5 y
Walcott ⁸²	2014	44	52.3	12 ^a	4.5 ^a	15.9 ^e	2.3	15.5 ^a	52 ^a	40.9 (7.41)	Median follow-up
Yen ⁸³	2010	186	47.31	12.7 ^b	3.2 ^b	36 ⁿ	0.54	21.9 ^b	98.4 ^b	49.5 (3.67)	5 y
Yeon ⁸⁴	2011	39	46.15	13 ^a 12.2 ^b	1.5 ^a 4.32 ^b	10.3 ^c	NR	21.2 ^b	45 ^a	38 (7.77)	5 y
Zabel-du Bois ⁸⁵	2006	22	50	11.8 ^b	4.2 ^a	35.5 ^o	NR	18 ^a	37.2 ^a	65 (10.17)	4 y
Zadeh ⁸⁶	2007	40	62.5	14.4 ^a 12 ^b	7 ^p	25 ^c	NR	NR	NR	66.7 (7.45)	3 y
Zeiler ⁸⁷	2016	19	47.37	14.2	3.1 ^b	15.8 ^q	10.5 ^q	19.5 ^b	62 ^b	81.8 (8.85)	5 y

Abbreviations: NR, not reported; RT, radiotherapy.

^aReported as the median.

^bReported as the mean.

^cEmbolization plus surgery.

^dPer the article, 3.3% underwent surgery, 18% underwent embolization, and 9.1% underwent both.

^eEmbolization alone.

^fPer the article, 11 of 53 patients (20.8%) underwent surgery, 5 patients (9.4%) underwent embolization, and 1 patient (1.9%) underwent both.

^gPer the article: "Twenty-seven patients (55.1%) had other treatment before radiosurgery: embolization, $n = 14$ (31.1%); neurosurgery, $n = 9$ (20.5%); embolization and neurosurgery, $n = 3$ (6.1%)."

^hPer the article, 2 patients (2%) underwent radiosurgery and 3 patients (3%) underwent combined surgery-radiotherapy.

ⁱCalculated average.

^jObliteration rate after second radiosurgery; obliteration rate at 4 y after initial radiosurgery was 65%.

^kPer the article, 12 patients (12%) underwent surgery, 18 patients (18%) underwent embolization, and 2 patients (2%) underwent both.

^lPer the article, 1 patient (4.5%) underwent surgery, 2 patients (9.1%) underwent embolization, and 1 patient (4.5%) underwent both.

^mAll patients underwent combined embolization and stereotactic radiosurgery.

ⁿPer the article: 24 patients (12.9%) underwent surgery, 38 patients (20.4%) underwent embolization, and 5 patients (2.7%) underwent both.

^oPer the article: 1 patient (4.5%) had prior surgery, 5 patients (22.7%) had prior embolization, and 2 patients (8.3%) had both.

^pReported as the average.

^qPer the article: prior treatments included "attempted surgical resection followed by embolization in [1] patient (5.35%), attempted embolization alone in [2] patients (10.5%) and GK at a different center in [2] patients.

average patient age was 16.11 years. The average tumor volume was 2.92 cm³, 81.2% had undergone prior surgery, 12.88% had undergone prior radiotherapy, and the average SRS dose was 13.47 Gy. The average follow-up duration was 53.22 months.

The rate of LC for all benign tumors was 89% (95% CI, 82%–95%), as shown in the forest plot in [Supplementary Figure 2](#). Meta-regression for LC showed no significant association with female sex ($P = .278$), average age ($P = .757$), average tumor size ($P = .927$), prior surgery ($P = .323$),

prior radiotherapy ($P = .652$), mean SRS dose ($P = .713$), or follow-up duration ($P = .560$).

Malignant Tumors

When malignant tumors were isolated (medulloblastoma, ependymoma, and high-grade glioma), 67.32% of patients were female, and the average age was 9.4 years. The average tumor volume was 3.05 cm³, 97.96% of patients had

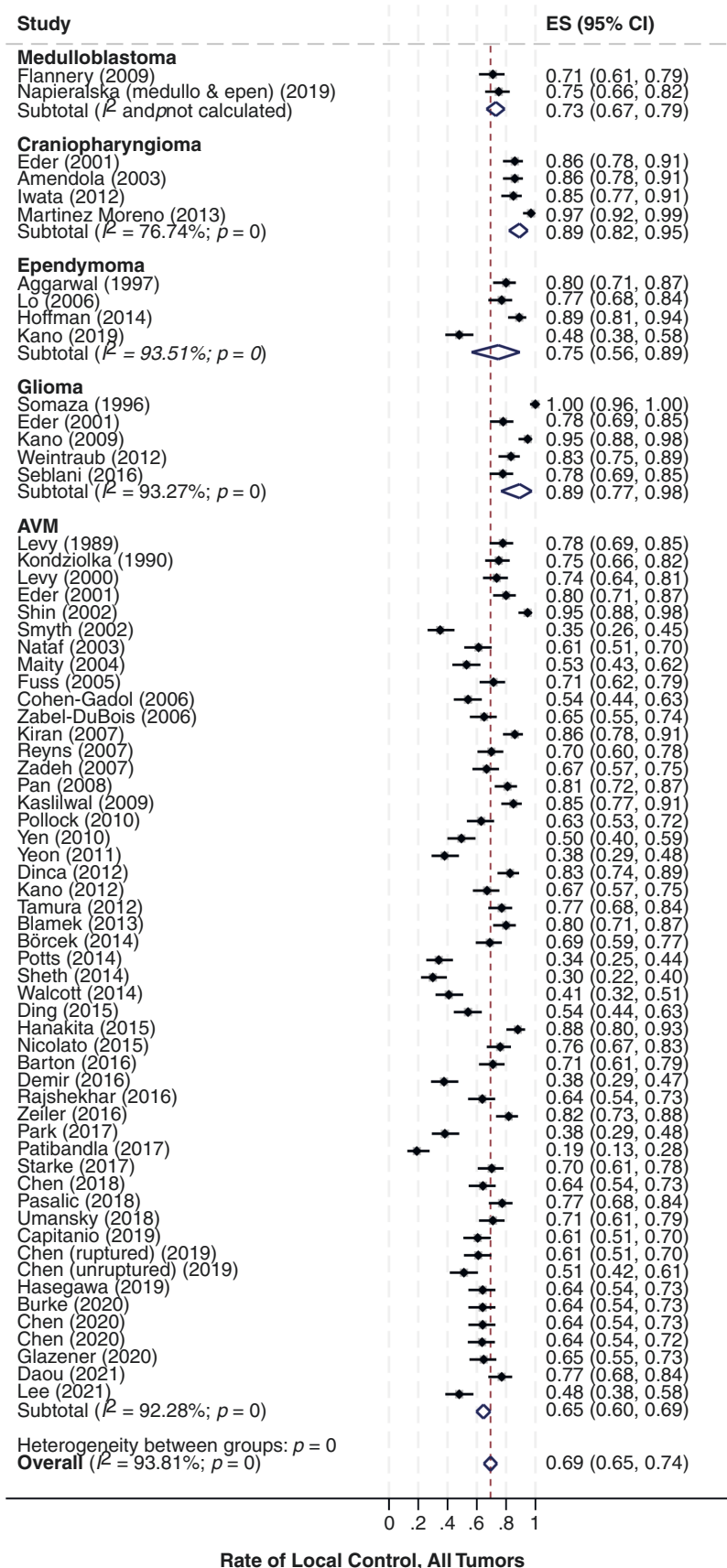


Figure 1. Forest plot showing the proportion of patients achieving local control (with 95% confidence intervals) using pediatric cranial stereotactic radiosurgery for medulloblastoma, craniopharyngioma, ependymoma, glioma, and arteriovenous malformation. Abbreviations: AMV, arteriovenous malformation; ES, effect size.

Table 6. International Stereotactic Radiosurgery Society Practice Guidelines for Pediatric Cranial Radiosurgery

	Recommendation	Single-Fraction SRS Dose (Gy)	Level of Evidence ^{a,c}
Benign Tumors			
	For pilocytic astrocytoma, a few series demonstrate durable local control; SRS may be considered when fractionated radiotherapy is not indicated.	12–24 ^a	4 ^b /Conditional (limited retrospective data)
	For craniopharyngioma, data are limited but there is a reasonable rationale to offer SRS for very small tumors (<3.5 cm ³) or tumors more than 3 mm away from the optic apparatus. ⁹¹	12–24 ^a	4 ^b /Conditional (limited retrospective data)
Malignant Tumors			
	For high-grade glioma, SRS may be considered at the time of recurrence, although data are limited.	15–24 ^a	4 ^b /Conditional (limited retrospective data)
	For ependymoma, SRS may be considered at the time of recurrence or for metastatic disease, although data are limited.	15–24 ^a	4 ^b /Conditional (limited retrospective data)
	For medulloblastoma, SRS may be considered at the time of recurrence or for metastatic disease, although data are limited.	15–24 ^a	4 ^b /Conditional (limited retrospective data)
	Toxicity related to SRS depends on prior treatment.	–	4 ^b
Arteriovenous Malformations			
	SRS should be considered as a definitive treatment.	18–24 ^c	4 ^b /Strong (significant retrospective data)
	Rates of obliteration are similar to those seen in adults.	–	4 ^b /Strong (significant retrospective data)
	Absence of embolization and higher margin SRS dose are associated with favorable outcomes. ⁵⁴	–	4 ^b /Conditional (limited retrospective data)

Abbreviation: SRS, stereotactic radiosurgery.

^aFor benign and malignant tumors, SRS dosing will be based on target size and proximity to critical structures. Adherence to normal tissue tolerances needs to be considered to determine whether SRS is appropriate. For larger tumors, or tumors close to critical structures such as the optic apparatus or brainstem, 3 to 5 fractions can be considered.

^bLevel 4: case series and poor-quality cohort and case-control studies.

^cFor arteriovenous malformations, dosing will be based on size; if an effective dose cannot be given safely in a single fraction, a staged approach can be considered.

undergone prior surgery, 97.02% had undergone prior radiotherapy, and the average SRS dose was 17.23 Gy. The average follow-up duration was 41.48 months.

As shown in the forest plot in [Supplementary Figure 2](#), the rate of LC for all malignant tumors was 71% (95% CI, 59%–82%). Meta-regression for LC showed no significant association with female sex ($P = .781$), average age ($P = .768$), tumor volume ($P = .836$), prior surgery ($P = .684$), prior radiotherapy ($P = .723$), average SRS dose ($P = .556$), or follow-up duration ($P = .579$).

All Tumor Types

When all patients (including those with AVMs) were combined, 49.92% were female, and the average age was 13.4 years (including adults). The mean target volume was 4.59 cm³, 41.55% had undergone prior surgery and/or embolization, 25.43% had undergone prior radiotherapy, and the average mean SRS dose was 18.93 Gy. The average follow-up duration was 58.02 months.

The rate of LC for all lesions, including AVMs, was 69% (95% CI, 65%–74%) ([Figure 1](#)). Meta-regression for LC showed no significant association of LC with female sex ($P = .191$), patient age ($P = .107$), average tumor size ($P = .852$), prior surgery ($P = .072$), prior radiotherapy ($P = .578$), average SRS dose ($P = .640$), or average follow-up duration ($P = .255$).

Discussion

There are several benefits to cranial radiosurgery for younger patients, including the delivery of a therapeutic dose of radiation in only 1–5 sessions. Limiting the number of fractions reduces anesthesia needs, minimizes the impact on daily routines, and allows for a quicker recovery.^{1,13} There is extensive evidence supporting SRS for multiple conditions in adults; however, the data specific to children are limited.¹³

This meta-analysis summarizes the pediatric cranial SRS data available for the treatment of benign and malignant tumors and AVMs. An additional indication for pediatric cranial radiosurgery is brain metastasis⁸⁸; however, data are limited for this indication. It is clearly apparent that the dominant use of pediatric SRS is for AVM. For the included indications, we were unable to identify predictive factors for LC due to limitations in the reporting of the evidence.

Medulloblastoma

Primary medulloblastoma in children is typically treated with surgery, chemotherapy, and craniospinal radiation with a tumor-bed boost dose.²⁴ Five-year overall survival in children with high-risk disease (ie, poor molecular features, <3 years of age, subtotal resection, metastasis at diagnosis) is under 70%.⁸⁹ The outcomes of recurrent medulloblastoma are poor—regardless of treatment modality—and recurrence is frequently fatal when children have had prior radiation therapy.^{24,90} SRS was first suggested as an option for recurrent or residual

medulloblastoma in the mid-1990s, and there are data showing the safety and potential efficacy in adults.²³ The best results (ie, longest survival, even though all patients eventually succumbed to their disease) were seen in patients who underwent repeat maximal resection (<1.5 cm³ residual tumor volume) and early adjuvant SRS.²³ The authors suggest that SRS may be of particular benefit for very young patients in whom fractionated radiotherapy is inadvisable because of the risk for neurotoxicity, and in patients with unresectable tumors (ie, critical brainstem structures or vasculature).²³

The recommendations for SRS in the setting of pediatric medulloblastoma, including doses, are limited to expert opinion ([Table 6](#)).

Craniopharyngioma

Results from the case series featured in this review show that SRS can be used safely for pediatric patients with craniopharyngioma; there were very few adverse effects involving the optic pathway or hypothalamic-pituitary system, and there were high rates of LC and neurocognitive preservation in the studies that evaluated the latter outcome.^{1,5,25–28} The authors of 1 series recommend using hypofractionated SRS for tumors that are large or located near the optic apparatus.²⁶ The authors of another series noted that SRS is “probably the treatment of choice” for smaller, primarily solid tumors with slowly progressive symptoms without severe visual effects.²⁵ One larger series found that SRS is well tolerated and that it does not interfere with other procedures that might be needed.²⁷

This modality may be particularly useful for craniopharyngioma, a tumor type that has a recurrence rate of greater than 25% after complete resection and between 50% and 100% after subtotal resection.⁵ Because SRS minimizes radiation doses to nearby normal tissue, and because craniopharyngiomas are typically responsive to radiation, this modality seems ideal for tumors that are not too large or not too close to the optic chiasm, optic nerve, and other critical neural structures.^{5,26} Less than 10 Gy seems to be the accepted safe dose for the optic apparatus^{1,5}; the authors of 1 series aimed to keep the optic chiasm dose < 8 Gy and the brainstem dose < 14 Gy, noting the minimal adverse effects with these parameters.⁵ In another series, 14% of patients had tumors > 10 cm³ and around 50% had tumors that were adjacent to the optical apparatus; their observed rates of visual disturbance and hypopituitarism were similar to those of other series that did not include these “riskier” patients.²⁶

This review found no significant association with LC and patient age for craniopharyngioma and no significant effect of prior radiotherapy or SRS dose. There were not enough data to assess for an effect of patient sex, tumor size, or prior surgery on LC.

Ependymoma

Standard treatment for ependymoma—surgical resection and adjuvant fractionated radiation therapy—has a significant failure rate; there are few options for recurrent disease.^{30,34,92} More than half of these tumors occur in patients

younger than 3 years of age, rendering the use of radiation riskier due to young patients' susceptibility to its adverse effects.³⁴ Because patients with gross residual disease after surgery have a poor prognosis, and because ependymoma does not respond well to chemotherapy, SRS is an attractive option, allowing for targeted treatment of the residual tumor with rapid dose fall-off peripherally.^{33,92}

In this review, patient age, prior radiotherapy, average SRS dose, and follow-up duration did not have an effect on LC for ependymoma. There was no significant effect on tumor size, although the range was not extensive, only varying by 1.2 cm³. There were not enough data to assess for an effect of patient sex or tumor size on LC.

Rates of LC ranged from 48% to 89% and were likely affected by the extent of resection, tumor grade, and the number of patients across the series.^{30,34,92} One series reported longer PFS after SRS than after initial radiation therapy.³⁴ Another noted significant morbidity and a lack of long-term disease control after SRS for recurrent ependymoma (after prior surgery and radiation therapy).³⁴ A third noted "reasonable" LC but tumor progression outside the SRS field.³³ The authors concluded that SRS is feasible and safe for unresectable gross disease, postsurgical gross residual disease, or postradiation gross recurrence. A small study suggested SRS as an option for salvage therapy for recurrence in the posterior fossa, and the authors of 2 other included studies agreed with the recommendations for residual and recurrent disease, noting that smaller tumors and later recurrence have the best response to SRS.^{31,32,92} Given that recurrent ependymoma has an overall survival rate of just 29% at 2 years,³⁰ SRS may be a reasonable option for salvage therapy and requires further study.

Glioma

The most common radiosurgery indications for benign tumors include treatment of surgically inaccessible masses, adjuvant therapy for less than gross total resection, and treatment for recurrence. Pilocytic astrocytoma can be definitively treated with surgical resection alone. However, adjuvant fractionated radiotherapy, targeted therapy, or chemotherapy are considered in the setting of less than gross total resection. Interestingly, a multicenter review of single-session radiosurgery for pilocytic astrocytoma demonstrated improved outcomes for patients treated at less than 18 years of age or when there was no prior radiotherapy or chemotherapy.⁹³ This suggests consideration of radiosurgery, either as an upfront adjuvant tool or as an option at the time of recurrence, when fractionated radiotherapy is not indicated. There are several studies with 8–15 years of follow-up (including 2 featured in this review) that demonstrate excellent LC (80%–100%) after using SRS for children with pilocytic astrocytoma.^{35,40,94} These results compare well to those of a phase 2 trial of conformal radiotherapy for pediatric low-grade glioma that reported an LC rate of 84% after 7 years.⁹⁵ The authors of the 1 included review noted that patients with smaller low-grade gliomas had better outcomes than those with larger lesions.⁴⁰

There are fewer data points available for high-grade glioma, but the role of SRS can be extrapolated from the

adult evidence where SRS is used in the setting of recurrence. Improved survival is observed, along with a more favorable safety profile than repeat surgical resection.¹⁸ One small series (7 children) included in this review found clinical improvement and no severe treatment-related adverse events after fractionated SRS for primary disease.⁴⁰ Another series that included 12 children with high-grade residual or recurrent glioma noted no permanent treatment-related complications.¹

All the glioma data in this review came from single-institution retrospective reviews that used a variety of SRS doses and fractionation schemes. One study showed an LC rate of 95% at 12 years. In this series, 50% of patients had a decrease in tumor size after treatment, with a 21% rate of complete remission.⁴⁰ However, our overall analysis did not find any significant patient-, tumor-, or treatment-related variables that affected LC. This lack of significant findings may be related to the limited number of patients.

Arteriovenous Malformation

Obliteration rates for SRS used to treat AVM were around 80% in this review, although it was challenging to compare outcomes across studies because various imaging techniques were used (eg, angiography, magnetic resonance imaging, and magnetic resonance angiography). Long-term data show safety and efficacy in adults; some researchers also consider it safe for children, although there is a lack of consensus.^{44,51,53} Some sources are a bit more guarded in endorsing the safety of pediatric patients, noting that it is "relatively safe" for patients in whom surgery would be too risky. It is worth noting that pediatric patients are a special population because the small yearly risk for rupture extends over many decades.⁴⁴

Although an International Radiosurgery Research Foundation project found a significantly better rate of AVM obliteration with doses ≥ 22 Gy,⁵⁴ the overall analysis of this systematic review did not find a statistically significant correlation between SRS dose and LC. It was notable, however, that the average dose was slightly higher (21.01 vs 20.36 Gy) in the studies with a higher rate of LC ($\geq 65\%$). The ISRS radiosurgery guideline for Spetzler–Martin grades I and II AVMs describes the estimated probability of total obliteration as 65%–70% at 15 Gy, 75%–80% at 18 Gy, and 85%–90% at 20–25 Gy.⁹⁶

Toxicity

Toxicity in this meta-analysis ranged substantially between patient series and tumor type.^{30,34–36,38,92} Toxicity appeared to depend on prior treatment, but data were not collected in a standard fashion across studies. A study by Hodgson et al included patients with recurrent or residual medulloblastoma, ependymoma, glioblastoma, and anaplastic astrocytoma. The authors noted an overall reoperation rate of 37%; 26% had symptomatic radiation necrosis requiring reoperation. They concluded that long-term neurologic outcomes vary widely and depend on the individual tumor type and additional therapies.² A review of an international consortium identified 36 pediatric patients in whom single-session SRS was used

for pituitary adenomas secreting adrenocorticotrophic hormone or growth hormone. The authors found new pituitary-hormone deficiency in 7 patients (19.4%) at a median time of 18 months after treatment (median endocrine follow-up, 63.7 months); they noted that longer follow-up is needed to identify delayed hypopituitarism. Two of the 24 patients with Cushing disease underwent subsequent repeat surgery; one of these underwent repeat SRS before reoperation. Three of the 12 patients with acromegaly required repeat SRS.⁹⁷

The 2 studies of medulloblastoma included in this review noted no instances of serious adverse radiation effects.^{23,24} Nonincluded studies of SRS specifically for medulloblastoma show varying incidences of toxicity; it is worth noting that most patients in these series had undergone prior surgery, craniospinal irradiation, or chemotherapy.^{2,98–101} One patient who received SRS plus chemotherapy for recurrent medulloblastoma experienced brainstem necrosis resulting in quadriplegia.⁹⁸

In the 6 studies on craniopharyngioma, with a total of 137 patients, there was only a single patient with new-onset hypopituitarism (it was not specified whether this was an adult or pediatric patient).²⁶ There were no other reported new-onset endocrinopathies, optic neuropathies, or cognitive delays; all adverse events in these areas were attributed to prior therapy.^{1,5,25,27,28} However, longer follow-up would be appropriate for many of these endpoints.

The most dramatic toxicity in this review was seen in 1 series of pediatric patients with recurrent ependymoma, with 1 patient death occurring from radiation necrosis and significant brainstem toxicity noted. In this series, the authors noted that morbidity from SRS can result years after treatment.³⁴ Another series of 12 pediatric patients with recurrent ependymoma noted radiation necrosis in 50%, although only half of these were symptomatic.³⁰ A third series noted only a single subacute reaction to SRS.²⁹ In the studies included in this review, the rate of toxicity ranged from 9.5% to 100%.^{30,34,92} Nonincluded studies of SRS for ependymoma show an incidence of toxicity ranging from 8% in each of the 2 patient series (recurrent ependymoma) to a 37% rate of reoperation in patients with recurrent or residual disease.^{2,102,103} Most patients had undergone prior surgery and radiation therapy, with maximal safe resection at the time of recurrence. Treatment failures were both local and distant.

The studies on low-grade glioma included in this review showed mostly minor, temporary adverse effects of SRS.^{1,35,36,40} In patients undergoing SRS for low-grade glioma, the rate of reported toxicity ranged from 0% to 44%.^{35,36,38,40} The most commonly reported toxicities were transient edema and cyst enlargement; not all patients were symptomatic. Data from nonincluded patient series of SRS for low-grade glioma show rates of toxicity ranging from 0% to 51%, with transient edema and cyst enlargement the most commonly noted complications.^{94,104–107}

The toxicity of SRS used for AVM was well-illustrated in a large study by Chen et al that included a pediatric and an adult cohort.⁴⁶ Radiation-induced changes were noted in 38% of the entire study population, but only 10% were symptomatic; the numbers were only slightly lower when limited to patients with single-session SRS (37% and 9%). Post-SRS hemorrhage occurred in 8% of

the study population, compared with 5% of the single-session cohort. Six percent of patients experienced permanent symptoms (5% of those with single-session SRS). Delayed cyst occurred in 2%, with 0.4% requiring intervention.⁴⁶

Limitations

There were several limitations to this analysis. Most of the included studies used single-fraction SRS, allowing for easy analysis of dose-per-fraction, but a few studies reported on single- and multiple-fraction SRS. For the latter, we used the median single-fraction dose for analysis. Because most of the included studies did not provide individual-level data for an analysis of LC vs dose, we used the average dose reported for each study. It was also difficult to identify specific trends in LC over time because the data were limited for all of the diagnoses except AVM. For AVM, the doses were too heterogeneous (ie, based on lesion size) to identify outcome trends over time. Unfortunately, we were not able to estimate LC at specific time points (eg, 1 year, 2 years, and 5 years) because each study reported outcomes at different times, and some studies did not specify a timeline or duration of LC. We were also unable to provide a toxicity analysis with our results because of limited data, heterogeneous reporting, and a lack of toxicity reporting in some studies. Finally, we acknowledge limitations in the statistical analyses used to account for missing data in average ages and doses. By definition, a meta-analysis converts the outcomes of different studies to a common measurement that can then be averaged across studies¹⁰⁸; it does not account for irregularity of distribution due to disease-specific age ranges of presentation or institution-specific (ie, nonstandardized) dosing protocols.

Conclusions

Pediatric SRS appears to provide acceptable rates of LC for a range of cranial tumors and AVMs, with normal tissue sparing that can significantly benefit younger patients. The toxicity seems minimal overall, with the significance of treatment-related adverse events often linked to prior therapies, although the data are sparse. Currently, the role of SRS for pediatric brain tumors seems to be limited but likely expanding. This review did not find any patient, tumor, or treatment characteristics significantly associated with LC.

Table 6 provides a summary of the authors' consensus guidelines for ISRS, regarding the judicious use of cranial SRS in pediatric patients. Prospective studies or an international database are needed to improve the current state of knowledge.

Supplementary material

Supplementary material is available online at *Neuro-Oncology* (<https://academic.oup.com/neuro-oncology>).

Keywords

arteriovenous malformations | brain neoplasms | pediatric | stereotactic radiosurgery

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Conflict of interest statement

None declared.

Author contributions

Conception of the initial draft, E.S.M.; statistical analyses, A.S., M.A.A.; authoring of statistical analysis section, A.S., M.A.A.; manuscript review, A.S., J.R., M.L., L.F., A.G., L.M., B.P., S.Y., J.S., I.P., J.H.S., R.K.; data review, S.Y., J.S.; authoring of consensus recommendations, E.S.M.

Data availability

The data used in this review will be made available from the Covidence system (<https://app.covidence.org/reviews/216737>) upon reasonable request.

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