Efficacy and Safety of Primary Stereotactic Radiosurgery in Patients With Intraventricular Meningiomas

Sebastian M. Christ, MD, PhD,a,* Dara S. Farhadi, MS,b Sun Junzhao, MD,c Anand Mahadevan, MD,d Maximilian Thormann, MD,e Fred C. Lam, MD, PhD,f Xin Yu, MD, PhD,g and Ekkehard M. Kasper, MD, PhDf

aDepartment of Radiation Oncology, University Hospital Zurich, University of Zurich, Zurich, Switzerland; bUniversity of Arizona College of Medicine — Phoenix, Phoenix, Arizona; cDepartment of Radiation Oncology, PLA General Hospital, Beijing, China; dGeisinger Medical Center, Radiation Oncology, Danville, Pennsylvania; eDepartment of Neuroradiology and Radiology, University Hospital, Magdeburg, Germany; fDivision of Neurosurgery, McMaster University and Hamilton General Hospital, Ontario, California; and gDepartment of Neurosurgery, PLA General Hospital, Beijing, China

Received 1 August, 2022; accepted 30 September, 2022

Abstract

Purpose: Primary stereotactic radiosurgery for intraventricular meningiomas remains controversial owing to the potential for life-threatening peritumoral edema and lack of long-term follow-up data. We review the literature and present the largest series to assess efficacy and safety of primary stereotactic radiosurgery.

Methods and Materials: A systematic review of the literature for primary stereotactic radiosurgery for intraventricular meningiomas was conducted. The retrospective series presented here comprised 33 patients who received primary stereotactic radiosurgery between 1999 and 2015 for a radiologically detected intraventricular meningioma. Demographic, diagnostic, and therapeutic data were extracted from medical records, imaging, and treatment-planning systems. Both standalone and pooled analysis were performed.

Results: The mean patient age was 53 years, and 24 patients (73%) were female. The median Karnofsky performance status pretreatment was 80 (range, 60-100). The majority of lesions were located in the lateral ventricles (n = 32; 97%). The mean tumor volume was 8.7 cm³ (range, 0.6-44.55 cm³). The mean delivered dose was 1390.9 cGy. Complete imaging follow-up data were available for 21 patients (64%). Of those, 14 (67%) showed partial or marginal response, 7 (33%) had stable disease, and no patient progressed per Response Assessment in Neuro-Oncology criteria. On last follow-up, 32 patients (97%) had significant improvement in performance status and a decrease in pretreatment symptoms. No high-grade Common Terminology Criteria for Adverse Events (version 5.0) toxicity was observed with the dose range employed.

Conclusions: Primary stereotactic radiosurgery for intraventricular meningiomas shows excellent treatment efficacy and low toxicity in patients with a long follow-up period. The best therapeutic algorithm remains to be established leveraging further clinical investigation.

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Introduction

Intraventricular meningiomas (IVMs) are a rarity. The first IVM was reported by A. Shaw in 1854 during an autopsy.⁷ Sixty-two years later, in 1916, H. Cushing became the first neurosurgeon to report on the successful resection of an IVM in a patient who went on to live for more than 2 decades.² Even though meningiomas are the most common benign brain tumor in adults, most neurosurgeons never see nor operate on patients with IVMs during their entire career. Evidence suggests that 0.5% to 3.7% of all intracranial meningiomas are IVMs.³⁷ A recent systematic review found IVMs to be slightly more prevalent in women.⁸ Like meningiomas, most IVMs are considered benign, with most being considered a World Health Organization grade of 1.⁸ IVMs are slow-growing tumors, which are derived from the meningotheial cells of the arachnoid layer and may present with the characteristic tail on magnetic resonance imaging (MRI).¹ Like most meningiomas, IVMs are typically asymptomatic until they reach considerable size, pushing into eloquent brain or vital vascular structures, which will then cause symptoms such as weakness from compression of the motor pathways.⁸ However, most patients present with symptoms of increased intracranial pressure, including headaches, blurred vision, visual field defects, memory loss, or seizures due to obstructive hydrocephalus caused by trapping and enlargement of the ventricles by the lesion.⁸

The location and pattern of growth of IVMs makes treatment very challenging. There is currently a lack of standard-of-care treatment algorithms for IVM, ranging from observation, resection alone, radiation therapy alone, or resection plus adjuvant radio- or chemotherapy.¹⁰ Upfront stereotactic radiosurgery (SRS) as a single treatment modality for IVMs remains controversial, as the development of life-threatening peritumoral or panhemispheric edema has been observed.¹¹,¹² In this systematic review and pooled analysis, we present a new cohort of 33 patients with IVMs treated with upfront SRS in light of a review of the literature on IVMs treated with SRS alone. To the best of our knowledge, our study represents one of the largest cohorts known to date having received primary SRS for treatment of their IVMs.

Methods and Materials

Systematic review of the literature and pooled analysis

PubMed, Science Direct, Embase, Cochrane, Springer Link, and Google Scholar were reviewed for articles reporting on the use of primary SRS for IVMs published between January 1991 and December 2021 by 1 author. The following terms were used to scan available titles and abstracts: CyberKnife, GammaKnife, meningioma, intraventricular meningioma, radiosurgery, radiotherapy, SRS, stereotactic radiotherapy, surgery, stereotactic irradiation, stereotactic radiosurgery, and ventricle. The Boolean operator “AND” was employed to combine search terms. Duplicate publications stemming from the search of different databases were excluded. Subsequently, the search results were reviewed by 2 investigators and filtered against our inclusion criteria. The publications that were retained (1) had abstracts available, (2) concerned the human species, (3) looked at patients aged 18 years or older, (4) were available in English, and (5) were published in a scientific journal. Lastly, all selected articles—and where no full text was available, the abstracts were screened by 2 team members—were reviewed against our exclusion criteria. To allow for a sensible assessment and comparison of treatment outcome and toxicity profile, articles that were kept for final further full-text analysis were clinical cohort studies, clinical trials, or case reports with sufficiently granular demographic data, diagnostic and therapeutic data, and ample follow-up data. Following the literature search, we applied the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic literature research.

Patient cohort

The radio-oncological treatment log of a large tertiary referral center for neuro-oncology was reviewed for patients with IVMs by 2 researchers. A total of 33 patients were identified, who received diagnoses of a solitary IVM using MRI, where in T1-weighted sequences lesions displayed the classic radiologic signs for IVM diagnosis, for example, isodense, uniform contrast-enhancement, and nearly circumferential T2 signal of cerebrospinal fluid. All patients subsequently underwent primary SRS with a GammaKnife between January 1991 and December 2015. Data regarding patient demographics, clinical symptoms, and diagnostic and treatment parameters were manually extracted from medical records, the neuro-oncology imaging repository, and the treatment-planning systems by 2 researchers.

SRS treatment

GammaKnife SRS was performed as an ambulatory procedure in all patients. Rigid fixation occurred via a Leksell stereotactic frame. Contours of target volumes and organs at risk were created by the treating primary oncologist. During planning, a highly conformal planning target volume coverage and sharp dose fall-offs were implemented. As is common in Leksell GammaKnife treatments, dose was prescribed to the 50% isodoseline. The Leksell GammaPlan software was used for planning, and plan as well as treatment quality control were effectuated by the treating...
primary oncologist and the responsible medical physicist. All SRS treatment procedures were safely administered and completed as planned.

**Follow-up and response assessment in our own clinical cohort**

Due to the large referral area to the treatment center, 12 patients (36%) who had returned to their home after SRS could not be fully assessed during routine clinical follow-up. However, a significant number of patient data (21 of 33; 64%) was available for detailed follow-up review, which included regular clinical examination and complete MRI imaging at 3-, 6-, or 12-month intervals. Imaging findings were assessed by independent, board-certified neuroradiologists; complex cases were discussed with at least 1 other neuroradiologist. Response assessment for the purposes of this study was MRI based. Two researchers conducted the response assessment in concordance with the proposed Response Assessment in Neuro-Oncology (RANO) and endpoints for meningioma clinical trials by the Neuro-Oncology Working Group published by Huang et al.\textsuperscript{13} Data on corticosteroid use were not available for the studied cohort, which is why patients with stable imaging studies and a clinical deterioration were classified as nonevaluable as per RANO recommendation.\textsuperscript{13} The reported tumor response assessment stems from the last available follow-up visit with imaging films.

**Data collection and statistical analysis**

Clinical, diagnostic, and therapeutic data were initially gathered in the spreadsheet application Microsoft Excel (version 16.0). Summary statistics for all variables under study were subsequently calculated using the commercially available statistical software package STATA (version 16.1; StataCorp). Images and figures were extracted from the neuro-oncology imaging repository and the treatment-planning systems. This retrospective study was approved by the responsible institutional review board before study initiation.
Results

Summary of findings from the scientific literature

A total of 1114 publications were identified in the literature after applying our predefined search criteria. After removal of duplicate publications, 364 original articles remained. Of those, 188 articles met our predefined inclusion criteria. After screening of these full text articles or abstracts against our predefined exclusion criteria, 6 articles were retained for detailed assessment and comparative analysis (for a detailed overview, see Fig. 1). The 6 identified studies were published between 1999 and 2016. They comprised 1 clinical study featuring 9 patients, 1 case series reporting on 2 patients, and 4 case studies detailing the case of 1 patient each.

| Data variables                                    | Patients (n = 33) |
|--------------------------------------------------|------------------|
| Age at primary diagnosis (y), median (range)     | 58 (20-71)       |
| Female sex, n (%)                                | 24 (73)          |
| KPS at first consult, median (range)             | 80 (60-100), n = 32 |
| Symptoms on initial presentation, n (%)          |                  |
| Headache                                         | 16 (49)          |
| Dizziness                                        | 10 (30)          |
| Nausea                                           | 6 (18)           |
| Epilepsy                                         | 6 (18)           |
| Blurred vision                                   | 4 (12)           |
| Amnesia                                          | 2 (6)            |
| Unsteady walk                                    | 2 (6)            |
| Vomiting                                         | 2 (6)            |
| Numbness                                         | 1 (3)            |
| Drowsiness                                       | 1 (3)            |
| Glossolalia                                      | 1 (3)            |
| Tumor location, n (%)                            |                  |
| Right trigone                                    | 17 (52)          |
| Left trigone                                     | 7 (24)           |
| Left lateral ventricle                           | 2 (6)            |
| Right posterior horn                             | 3 (6)            |
| Left posterior horn                              | 1 (3)            |
| Midline fourth ventricle                         | 1 (3)            |
| Right lateral ventricle                          | 1 (3)            |
| Right inferior horn                              | 1 (3)            |

Abbreviation: KPS = Karnofsky performance score.

Patient and tumor characteristics of our own patient series

The median age of the 33 patients under study was 58 years (range, 20-71), and 73% of the study participants (n = 24) were female. No patient had the genetic condition neurofibromatosis type 2. The Karnofsky performance status (KPS) at initial presentation was available for 32 of the 33 patients (97%), with the median KPS being 80% (range, 60%-100%). The 3 most common clinical signs and symptoms at initial presentation were headaches (n = 16, 49%), dizziness (n = 10, 30%), and nausea as well as epilepsy (both n = 6, 18%). The 3 most common tumor locations were the right trigone (n = 17, 52%), the left trigone (n = 8, 24%), and the left lateral ventricle as well as the right posterior horn (both n = 2, 6%). For a summary of patient characteristics, consult Table 1. Examples of diagnostic imaging films from this patient cohort are displayed in Fig. 2.
Treatment characteristics of our own patient series

For 30 of the 33 patients (91%), all treatment-specific imaging and radiation therapy data were available. The median tumor volume was 6.7 cm³ (range, 0.6-44.6). The administered mean dose was 1390.9 cGy (range, 1200-1600), with a median maximum dose in the center of the lesion of 2800 cGy (range, 2400-3300). For an example of a typical plan, target volume definition and dose-volume histogram of 1 of the cases, consult Fig. 3. The median treatment time was 1509 seconds (range, 593-2431). None of the patients developed acute toxicity from SRS—in particular, no patient experienced symptomatic hydrocephalus in the weeks after treatment. The median KPS of the 32 patients with available performance status data on the first consult after SRS was 90% (range, 60%-100%). Detailed clinical and imaging follow-up data were available for 21 of the 33 patients (64%). The median follow-up period was 7.9 years (range, 1.8-17.9). On the last clinical and imaging follow-up, no patient showed complete remission or progressive disease. Eight (38%) patients showed a partial response, and 6 (28%) patients showed a minor response. None of the 7 (33%) patients who had evidence of stable disease on imaging showed signs of clinical deterioration at the time of last consult. No Common Terminology Criteria for Adverse Events (version 5.0) toxicity grade 3 to 5 was observed—in particular, no patient developed a peritumoral edema 3 to 12 months after SRS. For an overview of treatment and follow-up data, see Table 2.

Results from pooled analysis

According to our systematic literature review, 5 patient series or case reports on SRS in patients with IVM were published to date, totaling at 47 patients including this patient series. The series of 33 patients presented here constitutes the largest available study thus far, reporting on patients with IVM who underwent primary SRS. Across all studies, mean patient age at primary diagnosis was 51 years, 66% patients (31 of 47) were female. Treatment schedules included primary SRS in almost all cases,
**Figure 3** (A) Exemplary target volume and isodose lines on axial and coronal scans. (B) Axial mid-lesion scan showing 6Gy, 9Gy, 12Gy and 15Gy isodose lines. (C) Corresponding dose-volume histogram (DVH).
with a mean prescribed dose of 15.5 Gy, mean of 1 fraction, and mean tumor volume of 7.86 cm³. Almost all patients for whom follow-up data were available after SRS (35 of 47; 74%) remained locally controlled (32 of 35; 91%). Toxicity reporting was not available in all studies. For a comparative view of selected studies, see Table 3.

### Discussion

Primary SRS has revolutionized the treatment of IVMs, as the deep location of these lesions and adjacent eloquent neurovascular structures present challenges to achieving a gross total resection. In this series, 100% of patients, for which complete follow-up data and imaging scans were available, remained locally controlled over a long follow-up period after SRS. Other SRS IVM studies have also reported high yet slightly lower control rates. Kim et al. in their analysis of 9 cases, reported local control in 7 of 9 cases (78%) after a mean follow-up of more than 5 years. Such local control rates are in line with and comparable to SRS after meningioma located in other parts of the brain, even in older patients. One challenge in interpreting and comparing local response rates across published IVM studies is the use of different response assessment criteria. In an attempt to contribute to the homogenization of response assessment for meningiomas, we followed the RANO criteria, making this study the first on IVMs to consistently apply these new criteria.

### Table 2  Treatment and follow-up characteristics

| Data variables                                      | Patients (n = 33) |
|----------------------------------------------------|------------------|
| Number of SRS treatments performed, n              | 33               |
| Tumor volume (cm³), median (range)                 | 6.7 (0.6-44.6), n = 30 |
| Administered dose (Gy), median (range)             | 14 (12-16), n = 30 |
| Maximum dose (Gy), median (range)                  | 28 (24-33.3), n = 30 |
| Treatment time (s), median (range)                 | 1508.6 (593.4-2430.6), n = 30 |
| KPS at first follow-up, median (range)             | 90 (60-100), n = 32 |
| Follow-up time (y), median (range)                 | 6.1 (1.8-17.9), n = 21 |
| Tumor treatment response, n (%)                    | n = 21           |
| Complete response                                  | 0 (0)            |
| Partial response                                   | 8 (38)           |
| Minor response                                     | 6 (28)           |
| Stable disease                                     | 7 (33)           |
| Progressive disease                                | 0 (0)            |

Abbreviations: KPS = Karnofsky performance score; SRS = stereotactic radiosurgery.

### Table 3  Comparative review of selected studies from the literature

| Study                  | Cases, n | Age (y), mean (range) | Female sex, n (%) | Treatment          | Mean dose (Gy) | Mean number of fractions | Volume (cm³), mean (range) |
|------------------------|----------|-----------------------|-------------------|-------------------|----------------|--------------------------|---------------------------|
| Current series         | 33       | 52 (20-71)            | 24 (73)           | Primary SRS       | 13.9          | 1                        | 8.7 (0.6-44.6)            |
| Nanda et al           | 1        | NA                    | NA                | Primary SRS       | NA            | 1                        | NA                        |
| Chen et al            | 1        | 41                    | 1 (100)           | SRS + shunt       | 16            | 1                        | NA                        |
| Nundkumar et al       | 2        | 50 (49-50)            | 2 (100)           | SRS + surgery*    | 18            | 1                        | 5.3 (3.5-7.2)             |
| Kim et al             | 9        | 51 (14-81)            | 3 (33)            | Mixed schedules†  | 17.5          | 1                        | 3.9 (0.8-11.8)            |
| Terada et al          | 1        | 58                    | 1 (100)           | Embolization + SRS| 12            | 1                        | 13.4                      |
| Total                 | 47       | 51                    | 31 (66)           | Mixed schedules†  | 15.5          | 1 (1-1)                  | 7.86                      |

Abbreviations: NA = not available; SRS = stereotactic radiosurgery; SRT = stereotactic radiation therapy.

* Microsurgical resection was performed because of clinical deterioration only.
† Treatment schedules included primary SRS, salvage SRS after recurrence, and adjuvant SRS after subtotal resection.
SRS for IVMs, which required the administration of steroids and even neurosurgical intervention. Additionally, one may rightly acknowledge that there may be some residual doubt in the absence of a histopathologic confirmation of the diagnosis. Other research groups have brought forward similar considerations. However, the authors acknowledge that there may be some residual doubt in the absence of a histopathologic confirmation of the diagnosis. Other research groups have brought forward similar considerations. Additionally, one may rightly note that IVMs can also present in other locations within the ventricle besides the trigone and the body, although much less frequently, and the authors are well aware that an imaging diagnosis indeed falls short of a tissue diagnosis. This will remain a challenge even in the era of ever-better imaging technology.

Limitations of this study include its retrospective nature and the limited sample size. Other limitations exist in the fact that follow-up data were not available for all treated patients, and information on corticoid use was not able for a complete response assessment according to the RANO criteria. However, as prospective data or trials will most likely never be available for such a rare tumor entity, similar studies constitute the only option to shed more light on the topic, and we recommend setup of a shared registry for this entity. Such a tumor registry could be hosted by one of the professional societies, such as the Radiosurgery Society of the United States, the World Federation of Neurosurgical Societies, or the NeuroPoint Alliance, Inc, to accrue a larger multicenter patient cohort for further investigation. This study presents the largest patient series ever published on the topic, and we consider strong points of this study that all data stem from 1 cancer center and that patients generally were treated and followed-up consistently and according to the same schedule.

Conclusion

Primary SRS for IVMs is a treatment option with very good treatment efficacy and low long-term toxicity in selected patients. Further investigation remains warranted to establish the best therapeutic algorithm for the tumors in this unusual location.

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