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Stereotactic radiosurgery for treatment of radiation-induced meningiomas: a multiinstitutional study

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OBJECTIVE Radiation-induced meningiomas (RIMs) are associated with aggressive clinical behavior. Stereotactic radiosurgery (SRS) is sometimes considered for selected RIMs. The authors investigated the effectiveness and safety of SRS for the management of RIMs.

METHODS From 12 institutions participating in the International Radiosurgery Research Foundation, the authors pooled patients who had prior cranial irradiation and were subsequently clinically diagnosed with WHO grade I meningiomas that were managed with SRS.

RESULTS Fifty-two patients underwent 60 SRS procedures for histologically confirmed or radiologically suspected WHO grade I RIMs. The median ages at initial cranial radiation therapy and SRS for RIM were 5.5 years and 39 years, respectively. The most common reasons for cranial radiation therapy were leukemia (21%) and medulloblastoma (17%). There were 39 multiple RIMs (35%), the mean target volume was 8.61 ± 7.80 cm^3, and the median prescription dose was 14 Gy. The median imaging follow-up duration was 48 months (range 4–195 months). RIM progressed in 9 patients (17%) at a median duration of 30 months (range 3–45 months) after SRS. Progression-free survival at 5 years post-SRS was 83%. Treatment volume ≥ 5 cm^3 predicted progression (HR 8.226, 95% CI 1.028–65.857, p = 0.047). Seven patients (14%) developed new neurological symptoms or experienced SRS-related complications or T2 signal change from 1 to 72 months after SRS.

CONCLUSIONS SRS is associated with durable local control of RIMs in the majority of patients and has an acceptable safety profile. SRS can be considered for patients and tumors that are deemed suboptimal, poor surgical candidates, and those whose tumor again progresses after removal.

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KEYWORDS stereotactic radiosurgery; radiation-induced meningioma; Gamma Knife; progression-free survival; safety; local control; oncology

ABBREVIATIONS CI = confidence interval; GKRS = Gamma Knife radiosurgery; HR = hazard ratio; IRRF = International Radiosurgery Research Foundation; NF1 = neurofibromatosis type 1; NF2 = NF type 2; OS = overall survival; PFS = progression-free survival; RIM = radiation-induced meningioma; RT = radiation therapy; SRS = stereotactic radiosurgery; WBRT = whole-brain RT.

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Radiation-induced meningiomas (RIMs) are the most common secondary intracranial neoplasms caused by ionizing cranial irradiation. They develop in patients who have undergone prior management of a brain tumor or leukemia or treatment for tinea capitis or in long-term atomic bomb survivors.[1–3] The latency period between cranial irradiation and RIM development may exceed 20 years, with a higher radiation dose being associated with a shorter latency period to tumor development.[2,4–6] RIMs arise within the treatment field of original cranial radiation therapy (RT), are histologically and radiographically distinct from previously irradiated brain tumors or lesions, and occur in patients without known genetic predisposition for brain tumors.[2,7–10] RIMs possess different genetic features than sporadic meningiomas;[2,11,12] compared with sporadic meningiomas, RIMs may have histological atypia, occur in multifocal locations, and increase in number during observation, thus making their gross-total resection and local tumor control more challenging.[2,8,13–15]

Resection is often considered an initial treatment for accessible RIMs, and it can be curative. However, complete resection of RIMs is often precluded by frequent presentation with multiple RIMs, involvement of osseous structures and blood vessels, aggressive and invasive growth patterns, and location in surgically inaccessible brain areas.[13,16–19] RT is often considered for the management of RIMs that are not amenable to complete resection.[10] Experience with stereotactic radiosurgery (SRS) for the management of RIMs remains limited due to the relative rarity of the disease. Prior published experience with SRS for RIM is limited to single-institution series, small sample sizes, and limited follow-up duration.[9,10,20] Further research is warranted to better define the safety and efficacy of SRS for the management of radiation-induced intracranial neoplasms. In this large, multicenter series of consecutive patients treated with SRS for RIMs, we investigated the effectiveness and safety of SRS for the management of RIMs.

Methods

Patients were identified from institutions affiliated with the International Radiosurgery Research Foundation (IRRF; protocol R-16-10) who were treated with SRS between 1990 and 2019. Data collection was approved by the IRBs at each of the participating centers. A database with variables of interest was established by investigators at the University of Virginia and sent to all participating centers. Individual patient data were de-identified and pooled for the analyses. In this study, we included patients who had a past history of cranial irradiation, were diagnosed with meningiomas based on MRI findings and/or histological examination (when available) with a latency period, had their RIM treated with SRS, had at least one clinical and radiological follow-up evaluation after SRS for RIM, and did not have a history of neurocutaneous disorders, such as neurofibromatosis type 1 (NF1) or type 2 (NF2), based on guidelines/practice at that center. MRI features of meningiomas included extraaxial location, dural involvement, and avid enhancement after gadolinium administration. Patients who originally underwent SRS, had WHO grade II or III meningiomas on histological examination, or had a history of neurocutaneous disorders such as NF1 or NF2 were excluded from the analysis. Thirty-two patients (61%) did not have meningioma surgery prior to the SRS and WHO grade was unknown.

In total, 60 eligible patients treated with SRS for RIM were identified in the IRRF database. The following centers contributed the data: the University of Pittsburgh Medical Center (19 patients), Université de Sherbrooke (10 patients), Ruber International Hospital (7 patients), University of Virginia Medical Center (6 patients), Na Homolce Hospital (5 patients), University of Pennsylvania (3 patients), Penn State Health–Hershey Medical Center (3 patients), Taipei Veterans General Hospital (2 patients), University of Southern California (2 patients), University of Alberta Hospital (1 patient), Mayo Clinic in Florida (1 patient), and Jewish Hospital, Mayfield Clinic (1 patient). Eight patients were excluded from the analyses because they were diagnosed with WHO grade II (n = 5) or grade III (n = 1) meningiomas or were originally treated with SRS (n = 2), leaving the final sample of 52 patients who were treated with SRS for histologically confirmed WHO grade I RIMs (n = 20, 39%) or presumed WHO grade I RIMs (n = 32, 61%) based on MRI findings and disease course.

Patient Evaluation

We obtained information regarding patient sex; age at first cranial irradiation; age at SRS for RIM; indication for first cranial irradiation; type, dose, and number of fractions of first cranial irradiation; history and extent (gross-total resection, subtotal resection, or biopsy) of pre-SRS resection and/or other RIM therapies preceding SRS; presenting symptoms; and RIM location. The latency of RIM development was defined as an interval (in months) from first cranial irradiation to RIM diagnosis or SRS. For those patients who underwent resection of a meningioma, we also obtained information about WHO grade of the resected meningioma.

SRS Technique

SRS was performed using model U, B, C, 4C, Perfexion, and Icon Gamma Knife units (Elekta AB) depending on technology availability at each of the participating centers at the time of SRS. Frame-based stereotaxy was performed using the Leksell model G frame (Elekta AB), in which the patient was placed under local anesthesia with or without conscious sedation. Frameless SRS using a thermoplastic mask was used for hypofractionated SRS (n = 2, 3%) or when stereotactic frame application was not technically possible. Radiosurgical planning was performed using high-resolution pre- and postcontrast T1-weighted MRI scans with 1-mm slick thickness. In rare cases in which MRI was contraindicated, stereotactic CT was used for SRS planning. SRS planning was performed by a multidisciplinary team that included a neurosurgeon, radiation oncologist, and medical physicist. At each center, planning was individualized based on patient needs and imaging findings. Radiosurgical parameters, including the margin and maximum dose, number of tumors treated,

treatment volume (cm^3), number of isocenters, and number of fractions, were recorded for each SRS session.

Clinical and Radiographic Follow-Up

Imaging and clinical follow-up was performed at approximately 6-month intervals for the first 2 years after SRS with subsequent annual follow-up thereafter. Imaging follow-up included T1-weighted contrast-enhanced and T2-weighted MRI. All follow-up imaging was reviewed by clinicians at the treating institution. Tumor volume on T1-weighted contrast-enhanced MRI on post-SRS surveillance studies was compared with that in the baseline pre-SRS study.

Clinical follow-up was obtained through a combination of outpatient clinic visits, inpatient admissions, and outpatient visits from referring primary care physicians. We recorded the interval (in months) from SRS for RIM to the last imaging follow-up, last clinical follow-up, or death. Patient neurological status at the last clinic follow-up visit was classified by the treating team as not changed, improved, or declined. We also recorded the presence, type, and timing of any new neurological deficits or other SRS-related complications. SRS-related adverse events were categorized according to the Radiation Therapy Oncology Group CNS toxicity criteria.[21]

RIM volume at last imaging follow-up was compared with the pre-SRS tumor volume and categorized as stable, regression, or progression. A volumetric increase of RIM by ≥ 20% from pre-SRS baseline brain MRI was defined as tumor progression, while a decrease of RIM volume by ≤ 20% was defined as tumor regression. Tumors with volumetric changes within 20% of the pre-SRS tumor volume were noted as stable disease.[22] Time to tumor volume change was also noted. The need for repeat SRS, radiotherapy, resection, or chemotherapy for RIM recurrence after the SRS, as well as time and cause of death, was recorded.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows (version 25.0, IBM Corp.). For all statistical tests, a p value < 0.05 was considered statistically significant. Overall survival (OS) of the study patients was defined as the interval (in months) from the start of index SRS for RIM to the last follow-up or death, and progression-free survival (PFS) was defined as the interval (in months) from SRS for RIM to the last imaging follow-up or MRI-documented tumor progression, whichever occurred first. The Kaplan-Meier method was used to calculate OS and PFS, and alive patients were censored at the last follow-up. The association of clinical and SRS treatment factors with OS and PFS was first investigated using univariate Cox regression analyses, and significant predictors in univariate analyses were subsequently entered into a multivariate Cox regression analysis model. The results of Cox regression analysis are presented as hazard ratios (HRs), 95% confidence intervals (95% CIs), and p values.

Results

Fifty-two patients (30 women and 22 men) underwent SRS for imaging-defined or confirmed WHO grade I RIM (Table 1) based on prior resection if one had been performed. The median patient age at the time of initial cranial RT was 5.5 years (range 4 months to 60 years), and the median age at the time of SRS for RIM was 39 years (range 12–75 years). The median latency period from original cranial irradiation to RIM development was 29 years (range 4–48 years). The most common reasons for cranial RT were leukemia (n = 11), medulloblastoma (n = 9), pituitary adenoma (n = 5), astrocytoma (n = 5), pineal mass/tumor (n = 4), and craniopharyngioma (n = 3). Twenty-one patients (40%) had prior meningioma resections. RIMs were most frequently discovered incidentally (n = 20, 39%). The most common neurological symptoms at the time of RIM diagnosis were seizure (n = 10) and focal neurological deficits (n = 14). The majority of patients harboring RIMs associated with seizures or focal neurological symptoms (n = 22) had convexity/parasagittal tumors (n = 16). Seven patients had multiple RIMs.

SRS Characteristics

Information from 60 SRS procedures (58 single-fraction SRSs and 2 hypofractionated SRSs) that were performed for 52 patients for RIMs were available for the analysis (Table 2). Sixty-five percent of SRS treatments were for solitary RIMs and 35% were for multiple RIMs. The mean target volume at each SRS procedure was 8.61 ± 7.80 cm^3 (median 6.20 cm^3, range 0.3–28.40 cm^3). In patients who underwent single-fraction SRS, the median prescription dose was 14 Gy (range 8–20 Gy). The median maximal dose was 26 Gy (range 16–55 Gy). The median time from initial cranial RT to SRS for RIM was 29 years (range 4–55 years).

Tumor Control

The median duration of imaging follow-up after SRS for RIM was 47.6 months (range 3.8–194.6 months; Table 3, Fig. 1A). At last imaging follow-up, the vast majority of the treated lesions were classified as stable (n = 22, 42%) or regressed (n = 19, 37%). Progression was documented in 9 RIMs (17%). The median time to tumor progression was 30 months (range 3–45 months). Thirteen patients received one or more additional treatments for index RIM after the initial SRS.

Actuarial PFS rates at 1, 2, and 5 years after SRS were 94%, 92%, and 83%, respectively. In univariate Cox regression analyses, greater age at SRS (p = 0.031), the presence of multiple RIMs (vs a solitary RIM; p = 0.038), and tumor volume ≥ 5 cm^3 (p = 0.047) were associated with increased risk for tumor progression. In the multivariate Cox regression model, treatment volume ≥ 5 cm^3 (HR 8.226, 95% CI 1.028–65.857, p = 0.047) emerged as an independent predictor of greater post-SRS progression risk of RIMs (Table 4, Fig. 2). PFS was similar in histologically confirmed versus imaging-defined WHO grade I RIMs (p = 0.83).

Clinical Outcomes

At the last follow-up visit, 39 patients were neurologically stable, 8 patients had declined, and 5 patients improved.

TABLE 1. Baseline patient characteristics

Characteristic	Value
No. of patients	52
Median age at first SRS, yrs (range)	39 (12–75)
Median age at first RT (range)	5.5 yrs (4 mos–60 yrs)
Median RIM latency, yrs (range)	29 (4–48)
Sex, n (%)	
Men	22 (42)
Women	30 (58)
Indication for initial RT, n (%)	
Leukemia	11 (21)
Medulloblastoma	9 (17)
Pituitary adenoma	5 (10)
Astrocytoma	5 (10)
Pineal mass/tumor	4 (8)
Craniopharyngioma	3 (6)
Tinea capitis	2 (4)
Pilocytic astrocytoma	2 (4)
Glioma	2 (4)
Meningioma	1 (2)
Ependymoma	1 (2)
Experimental	1 (2)
Germinoma	1 (2)
Langerhans cell histiocytosis	1 (2)
Oligodendroglioma	1 (2)
Retinoblastoma	1 (2)
Rhabdomyosarcoma	1 (2)
Subependymoma	1 (2)
Type of initial RT, n (%)	
WBRT	18 (35)
Other or unknown	34 (65)
Dose of initial RT, Gy	
Available data, n (%)	26 (50)
Median (range)	45 (10–64)
No. of fractions of initial RT	
Available data, n (%)	14 (27)
Median (range)	25 (1–36)
Resection prior to SRS, n (%)	21 (40)
Meningioma location, n (%)	
Convexity	43 (37)
Parafalcine	24 (21)
Cavernous sinus	7 (6)
Tentorial	7 (6)
Cerebellopontine angle	5 (4)
Sphenoid	3 (3)
Sellar/parasellar	3 (3)
Petroclival/petrous	3 (3)
Infratemporal	2 (2)
Clinoid	2 (2)
Other	16 (14)
Meningioma WHO grade, n (%)	
Histologically conformed WHO grade I	20 (39)
Radiographically defined	32 (61)
Presentation*	
Incidental finding	20
Headache	8
Seizure	10
Focal neurologic deficit	14
Data not available/other	4
Median KPS score prior to SRS (range)	90 (50–100)

CONTINUED IN NEXT COLUMN »

» CONTINUED FROM PREVIOUS COLUMN

KPS = Karnofsky Performance Scale.
* Total number > 52 because some patients had more than one symptom.

Of the patients who exhibited a neurological decline, 1 patient (13%) had tumor progression; of those who improved or remained stable, 48% had stable tumors and 36% had decreased tumor volume. Three patients (6%) developed new neurological symptoms (grade 4 CNS toxicities) after SRS that included gait impairment and leg weakness. Four patients (8%) experienced SRS-related complications that included intratumoral hemorrhage or T2 signal change. In 5 patients who developed a post-SRS complication and had available information about initial cranial RT, the median radiation dose was 35 Gy and ranged from 10 to 64 Gy. Indications for initial cranial irradiation in this group of patients included medulloblastoma (n = 2), pituitary adenoma (n = 2), craniopharyngioma (n = 2), and leukemia (n = 1). The mean latency period from SRS to a new neurological deficit or SRS-related complication was 30 ± 29 months (range 1–72 months). Age at RT, age at SRS, interval from RT to SRS, margin dose, maximal dose, and treatment volume were similar between patients who experienced a post-SRS complication or new neurological deficit compared with those who did not (all p values ≥ 0.22). Two patients died during post-SRS follow-up (Fig. 1B). One death was attributed to progression, and the underlying cause of death of the other patient was unknown.

Discussion

Our series exploring the safety and effectiveness of SRS for RIMs offers new insights into patterns of tumor control and failure from a multiinstitutional cohort. SRS was associated with durable local control of RIMs in the majority of patients and had an acceptable safety profile. Eighty-five percent of patients had stable or improved neurological status at the last follow-up, and 14% of patients developed new neurological symptoms or SRS-related imaging changes.

Our findings comprise the largest series of its type to date and indicate that SRS was associated with durable local control of RIM that was comparable to the local control rates known from prior reports of SRS for sporadic meningiomas. During a median imaging follow-up of 47.6

TABLE 2. SRS treatment of RIMs

Parameter	Value
Total no. of SRS procedures, n (%)	60
Single-fraction SRS	58 (97)
Hypofractionated SRS	2 (3)
Total no. of RIMs treated w/ SRS	108
Multiplicity of RIMs, n (%)	
Solitary	39 (65)
Multiple	21 (35)
Median no. of RIMs treated at each SRS treatment (range)	1 (1–10)
Target volume at each SRS treatment	
Median, cm^3 (range)	6.20 (0.3–28.40)
Volume ≥5 cm^3, n (%)	25 (42%)
Median prescription dose, Gy (range)*	14 (8–20)
Median maximal dose, Gy (range)	26 (16–55)

* Only patients who underwent single-fraction radiosurgery (n = 58).

TABLE 3. Tumor control and safety

Variable	Value
Median imaging follow-up, mos (range)	47.6 (3.8–194.6)
Tumor control rate, n (%)	
Stable	22 (42)
Regression	19 (37)
Progression	9 (17)
Data not available	2 (4)
Median clinical follow-up, mos (range)	46.91 (7.87–192.19)
Neurological status at last follow-up, n (%)	
No change	39 (75)
Improved	5 (10)
Declined	8 (15)
New post-SRS symptom or complication, n (%)	7 (14)
Median mos to new symptoms or complications (range)	30 (1–72)
Post-SRS treatments, n (%)	
Any treatment	13 (25)
Resection	9 (17)
Repeat SRS	4 (8)
Fractionated RT	2 (4)
Chemotherapy	1 (2)
Crude mortality, n (%)	2 (4)

months (range 3.8–194.6 months), 17% of patients experienced RIM progression that was documented from 3 to 45 months following SRS. PFS rates at 2 and 5 years after the SRS were 92% and 83%, respectively. The long-term local tumor control rate of RIMs in our series was comparable to local tumor control rates for sporadic meningiomas that usually exceed 85%.[23,24] The local RIM control rate in the present series was higher compared with the RIM control rate of 75% previously reported by Kondziolka and colleagues in a series of 19 patients with RIM treated with SRS, with a median follow-up of 44 months.[10] Another single-institution series of 12 patients with RIM treated with SRS and followed for a median interval of 35 months found that local tumor control was achieved in all treated patients, and there were 2 cases of distant tumor recurrence.[20] An additional single-institution series of 17 patients with RIM treated with SRS also reported a 100% 5-year local tumor control rate, with 1 treatment failure at 65 months after the SRS.[9] The current study and previously published studies strongly suggest that SRS allows durable long-term local disease control of RIMs in the majority of patients. However, due to late SRS treatment failures, long-term imaging surveillance should be considered after SRS of RIM. Another potential limitation is that it remains unknown whether RIMs that ultimately do undergo disease progression following SRS do so in a more aggressive or rapid way than their sporadic counterparts, or mechanistically whether additional radiation ultimately contributes to worsened chromosomal instability or mutational burden within the RIM.

Resection is often considered for initial management of RIM.[2,8] If technically possible, gross-total resection can be curative and surgery allows for the assessment of meningioma grade, which can be important for guidance of adjuvant therapies. Another benefit of open resection and tissue acquisition is to rule out other rare pathologies that may include hemangiopericytoma, lymphoma, solitary fibrous tumor, and others. However, gross-total resection of RIMs is not always possible because of frequent multiplicity, and invasion of osseous, vascular, or neural structures.[10] In our series, one-third of patients harbored multiple RIMs and half of meningiomas were in the skull base. SRS should be considered for patients harboring RIMs in difficult-to-access locations, those with multiple lesions, and those who are poor surgical candidates.[25] Depending on the location of the RIM, the planning of repeat conventional fractionated RT can be difficult in patients who have received prior wide-field RT without exceeding dose tolerances to critical normal structures, such as the optic nerves and chiasm. SRS allows spatially precise and conformal treatment of RIMs that helps to mitigate potential risks associated with wider treatment fields and low-dose wash (decreasing dose to surrounding structures) of fractionated RT approaches.

We excluded patients with histologically confirmed WHO grade II and III meningiomas because it is well established that they are more resistant to SRS therapy and have more aggressive clinical courses than WHO grade I tumors, and they often require multimodality treatment. However, a histological diagnosis was not available in 61% of the study patients. A higher WHO grade of meningiomas is associated with inferior local disease control and worse prognosis.[26] For example, the 5-year local control rate of WHO grade II non-RIMs ranges from 50% to 60%, and only 10% of WHO grade III non-RIMs are controlled with SRS.[27–29] These findings indicate that long-term control of RIMs can be inferior when compared with sporadic WHO grade I meningiomas, but superior to high-grade sporadic meningiomas. Indeed, the genetic and mutational landscape of RIMs is different from that

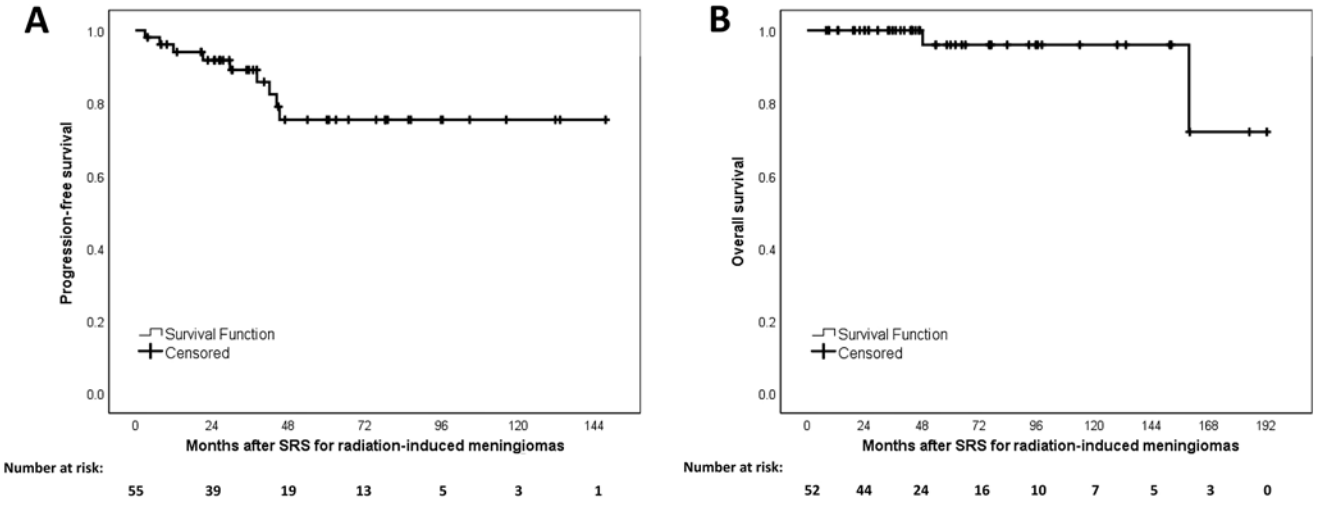

FIG. 1. Kaplan-Meier plots of PFS (**A**) and OS (**B**) in the study patients.

of sporadic meningiomas, which might have radiobiologic implications.[11,12] For example, RIMs had more common combined losses of chromosomes 1p and 22q as well as more complex chromosomal aberrations than sporadic meningiomas, while targetable mutations were less common.[11] Further studies are warranted to elucidate molecular characteristics and possibly identify treatment targets of RIM.

Treatment volume ≥ 5 cm^3 was an independent predictor of tumor progression after SRS in multivariate regression analyses. Greater patient age at SRS, the presence of multiple (vs solitary) RIMs, and treatment volume ≥ 5 cm^3 were associated with shorter PFS in univariate analysis. These findings correspond to the findings in a series from the University of Pittsburgh that reported that larger target volume was associated with shorter post-SRS PFS of RIM.[28] A literature review of RIMs treated with SRS found that tumors that failed after SRS were larger when compared with controlled tumors (10.7 cm^3 and 2.2 cm^3, respectively), while age, sex, and tumor grade were similar between the two groups.[20] Greater tumor volume is also associated with inferior local control of sporadic meningiomas with SRS.[28,30–34] Higher risk of progression after SRS should be considered for patients presenting with RIMs exceeding 5 cm^3, and this can also have implications for their follow-up frequency. This finding also suggests that earlier SRS when the RIM is smaller may portend a better long-term result for the patient.

Margin dose was previously implicated as a significant predictor of local control of RIMs[10] and sporadic meningiomas.[23,35] However, prescription radiation dose was not associated with local control of RIMs in the current study, which can be explained by the small sample size and small SRS treatment failure rate. The median prescription radiation dose in the present series was 14 Gy and ranged from 8 to 22 Gy. Comparable prescription doses from RIMs were previously reported by other groups, with median prescription doses of 13–14 Gy (range 8–20 Gy).[9,20,28] The prescription dose for RIMs corresponds to commonly used prescription radiation doses for sporadic WHO grade I meningiomas,[29] emphasizing that the usual radiation dose should be used to optimize the local control of meningiomas in patients with a prior history of cranial irradiation.

During the median clinical follow-up of 47 months (range 8–192 months), 3 patients experienced new neurological symptoms after SRS and 1 patient experienced

TABLE 4. Cox regression analysis of predictors of RIM progression after SRS

Predictor	Univariate Analysis	Multivariate Analysis
Age at RT	1.041 (0.998–1.087), 0.063	—
Age at SRS	1.054 (1.005–1.105), 0.031	p = 0.108
Latency btwn RT & SRS	1.017 (0.989–1.067), 0.497	—
Sex	0.906 (0.468–1.754), 0.769	—
Multiple RIMs*	4.379 (1.085–17.673), 0.038	p = 0.310
Treatment volume ≥5 cm^3	8.226 (1.028–65.857), 0.047	8.226 (1.028–65.857), 0.047
Prescription dose, Gy	1.096 (0.822–1.461), 0.532	—
Maximal dose, Gy	0.971 (0.860–1.097), 0.635	—

Data given as HR (95% CI), p value.
* Yes = 1 or no = 0.

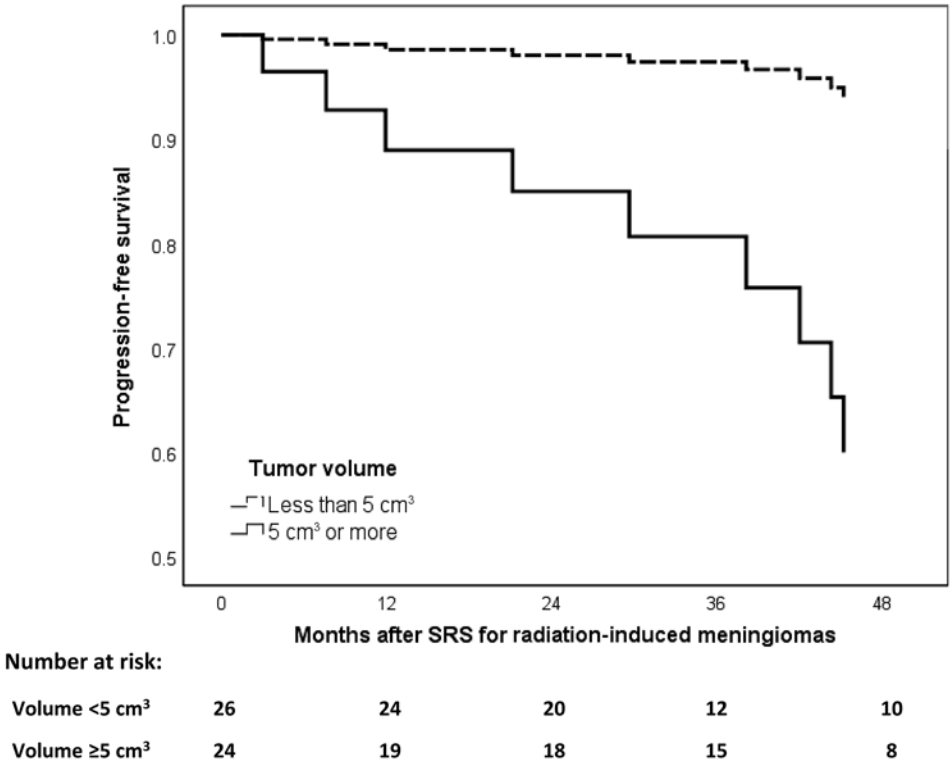

FIG. 2. Kaplan-Meier plots of PFS stratified by SRS treatment volume (< 5 cm^3 or ≥ 5 cm^3).

intratumoral hemorrhage. Radiological T2 signal changes without associated neurological decline were noted in 3 patients. Comparable rates (5.3%) of post-SRS morbidity and peritumoral imaging signal changes were noted in one prior study of Gamma Knife radiosurgery (GKRS) for RIMs.[28] Jensen and colleagues described 1 case (6% of all treated patients) of increased seizure activity after SRS for RIM that was associated with radiosurgery-related changes on imaging studies.[9] Another group noted a higher incidence of SRS toxicity in the setting of RIMs (n = 2, 17%) that occurred within 3–4 months after the SRS and included cranial nerve neuropathy and leg weakness/numbness.[20] The incidence rate of transient and permanent SRS-related neurological complications for meningiomas is below 10%, and as many as 40% of patients develop new or worsening post-SRS peritumoral edema.[36–40] These findings suggest that the safety profile of SRS for RIMs is comparable to the adverse event risk after SRS for sporadic meningiomas. Meticulous SRS planning is of paramount importance and should be exercised for complication avoidance.

In our series, RIMs were discovered incidentally in 39% of patients. Imaging surveillance is often recommended for incidentally discovered sporadic meningiomas.[41] However, a recent systematic review and meta-analysis reported significant variability in the management of incidental meningiomas that included active monitoring (50.7%), surgery (27.3%), and SRS (22.0%).[42] Patients with prior histories of cranial irradiation for various brain lesions are at elevated risk for the detection of small lesions such as RIMs that are asymptomatic, due to both the increased frequency of brain imaging for an index lesion and the known association between cranial irradiation and the development of RIMs. The management strategy of RIMs (observation vs active treatment) and timing should be selected considering RIM size, location, symptoms, prior therapies, ease of resection, and patient preference. It is expected that the threshold for initiating active treatment can be lower for RIMs versus sporadic tumors given the higher probability of more rapid progression, as well as the patient's prior history of a brain tumor, experience with cranial irradiation and often other treatments such as resection, and well-defined opinions regarding intervention based on their past personal experiences.

Study Limitations

This study has limitations typical of a retrospective, multicenter study of a rare intracranial tumor type. Foremost, numerous tumors in this study lacked pathological confirmation of being a WHO grade I meningioma and also lacked MIB-1 labeling data for RIMs. In the current study, inclusion of tumors lacking pathological confirmation that may have proven to be higher-grade meningiomas or ones with high MIB-1 labeling should only have biased the study outcomes toward less favorable PFS and OS following SRS. Initial cranial RT details were not available for all patients; this prevented us from independently evaluating cranial irradiation fields and dose, studying the association of initial cranial irradiation with RIM latency, and investigating the safety and effectiveness of subsequent SRS. We could not confirm whether presumed RIMs developed within the treatment field of initial cranial irradiation

for patients who did not receive whole-brain RT (WBRT). However, initial cranial irradiation was performed more than 2 decades ago when less sophisticated and conformal cranial irradiation methods were routinely used, raising the possibility of at least some degree of skull irradiation even in patients who did not receive WBRT. It is possible that increasing the use of intensity-modulated photon RT, which results in increased low-dose irradiation wash, could increase the risk of RIMs well outside the radiation fields. Furthermore, due to the longitudinal multicentered design of the study, both intra- and interinstitutional variation of RIM treatment strategies is expected because SRS treatment protocols varied between the 12 participating centers, and there have been improvements in SRS techniques and systems over the study period.[43] We also did not systematically evaluate growth trajectories of RIMs before the SRS treatment, nor did we capture race/ethnicity data. We expect that these variations had limited effect given that all patients were managed at experienced GKRS centers and according to the prevailing guidelines at the time of treatment. We cannot determine the effect of race/ethnicity on SRS outcomes. Further longitudinal follow-up of patients is required to better understand the long-term outcomes of SRS for RIMs. Also, while this study is the largest to date, additional patient accrual is needed in future studies to adequately power subgroup analysis to evaluate topics such as SRS for asymptomatic yet progressive RIMs. In addition, detailed SRS treatment protocols were reported by all participating centers. Due to possible differences in the natural course of RIMs secondary to proton versus photon therapy, our results cannot be generalized to RIMs developing after proton beam therapy, which is commonly used for treating pediatric patients.[44] Our large sample size of RIM, which is an extremely rare disorder, is an important strength of this study that fortifies the study findings.

Conclusions

SRS is associated with durable local control of RIMs in the majority of patients and has an acceptable safety profile that is comparable to that of SRS-treated sporadic meningiomas. SRS should be considered in the management of RIM in difficult-to-access areas and for poor resection candidates. Future studies exploring the safety and efficacy of surgical and SRS approaches of RIM, as well as the genetic landscape of RIM, are encouraged to identify optimal treatment approaches and to improve patient selection for this rare but challenging disorder.

References

1. Co JL, Swain M, Murray LJ, et al. Meningioma screening with MRI in childhood leukemia survivors treated with cranial radiation. *Int J Radiat Oncol Biol Phys*. 2019;104(3):640–643.
2. Umansky F, Shoshan Y, Rosenthal G, et al. Radiation-induced meningioma. *Neurosurg Focus*. 2008;24(5):E7.
3. Yamanaka R, Hayano A, Kanayama T. Radiation-induced meningiomas: an exhaustive review of the literature. *World Neurosurg*. 2017;97:635–644.e8.
4. Preston DL, Ron E, Yonehara S, et al. Tumors of the nervous system and pituitary gland associated with atomic bomb radiation exposure. *J Natl Cancer Inst*. 2002;94(20):1555–1563.
5. Sadamori N, Shibata S, Mine M, et al. Incidence of intracranial meningiomas in Nagasaki atomic-bomb survivors. *Int J Cancer*. 1996;67(3):318–322.
6. Shintani T, Hayakawa N, Kamada N. High incidence of meningioma in survivors of Hiroshima. *Lancet*. 1997;349(9062):1369.
7. Cahan WG, Woodard HQ, Higinbotham NL, et al. Sarcoma arising in irradiated bone: report of eleven cases. 1948. *Cancer*. 1998;82(1):8–34.
8. Harrison MJ, Wolfe DE, Lau TS, et al. Radiation-induced meningiomas: experience at the Mount Sinai Hospital and review of the literature. *J Neurosurg*. 1991;75(4):564–574.
9. Jensen AW, Brown PD, Pollock BE, et al. Gamma knife radiosurgery of radiation-induced intracranial tumors: local control, outcomes, and complications. *Int J Radiat Oncol Biol Phys*. 2005;62(1):32–37.
10. Kondziolka D, Kano H, Kanaan H, et al. Stereotactic radiosurgery for radiation-induced meningiomas. *Neurosurgery*. 2009;64(3):463–470.
11. Agnihotri S, Suppiah S, Tonge PD, et al. Therapeutic radiation for childhood cancer drives structural aberrations of NF2 in meningiomas. *Nat Commun*. 2017;8(1):186.
12. Shoshan Y, Chernova O, Juen SS, et al. Radiation-induced meningioma: a distinct molecular genetic pattern? *J Neuropathol Exp Neurol*. 2000;59(7):614–620.
13. Rubinstein AB, Shalit MN, Cohen ML, et al. Radiation-induced cerebral meningioma: a recognizable entity. *J Neurosurg*. 1984;61(5):966–971.
14. Sadetzki S, Flint-Richter P, Ben-Tal T, Nass D. Radiation-induced meningioma: a descriptive study of 253 cases. *J Neurosurg*. 2002;97(5):1078–1082.
15. Soffer D, Gomori JM, Siegal T, Shalit MN. Intracranial meningiomas after high-dose irradiation. *Cancer*. 1989;63(8):1514–1519.
16. Borovich B, Doron Y. Recurrence of intracranial meningiomas: the role played by regional multicentricity. *J Neurosurg*. 1986;64(1):58–63.
17. Borovich B, Doron Y, Braun J, et al. Recurrence of intracranial meningiomas: the role played by regional multicentricity. Part 2: Clinical and radiological aspects. *J Neurosurg*. 1986;65(2):168–171.
18. Jääskeläinen J. Seemingly complete removal of histologically benign intracranial meningioma: late recurrence rate and factors predicting recurrence in 657 patients. A multivariate analysis. *Surg Neurol*. 1986;26(5):461–469.
19. Wilson CB. Meningiomas: genetics, malignancy, and the role of radiation in induction and treatment. The Richard C. Schneider Lecture. *J Neurosurg*. 1994;81(5):666–675.
20. Kuhn EN, Chan MD, Tatter SB, Ellis TL. Gamma knife stereotactic radiosurgery for radiation-induced meningiomas. *Stereotact Funct Neurosurg*. 2012;90(6):365–369.
21. Shaw E, Scott C, Souhami L, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. *Int J Radiat Oncol Biol Phys*. 2000;47(2):291–298.
22. Yang D-Y, Sheehan J, Liu Y-S, et al. Analysis of factors associated with volumetric data errors in gamma knife radiosurgery. *Stereotact Funct Neurosurg*. 2009;87(1):1–7.
23. Sheehan JP, Starke RM, Kano H, et al. Gamma Knife radiosurgery for sellar and parasellar meningiomas: a multicenter study. *J Neurosurg*. 2014;120(6):1268–1277.
24. Sheehan JP, Williams BJ, Yen CP. Stereotactic radiosurgery for WHO grade I meningiomas. *J Neurooncol*. 2010;99(3):407–416.
25. Cohen-Inbar O, Lee CC, Schlesinger D, et al. Long-term results of stereotactic radiosurgery for skull base meningiomas. *Neurosurgery*. 2016;79(1):58–68.
26. Pollock BE, Jacob JT, Brown PD, Nippoldt TB. Radiosurgery of growth hormone-producing pituitary adenomas: factors

associated with biochemical remission. *J Neurosurg*. 2007; 106(5):833–838.
27. Ding D, Starke RM, Hantzmon J, et al. The role of radiosurgery in the management of WHO Grade II and III intracranial meningiomas. *Neurosurg Focus*. 2013;35(6):E16.
28. Kondziolka D, Mathieu D, Lunsford LD, et al. Radiosurgery as definitive management of intracranial meningiomas. *Neurosurgery*. 2008;62(1):53–60.
29. Pollock BE, Stafford SL, Link MJ. Stereotactic radiosurgery of intracranial meningiomas. *Neurosurg Clin N Am*. 2013; 24(4):499–507.
30. Ge Y, Liu D, Zhang Z, et al. Gamma Knife radiosurgery for intracranial benign meningiomas: follow-up outcome in 130 patients. *Neurosurg Focus*. 2019;46(6):E7.
31. Starke RM, Przybylowski CJ, Sugoto M, et al. Gamma Knife radiosurgery of large skull base meningiomas. *J Neurosurg*. 2015;122(2):363–372.
32. Park K-J, Kano H, Iyer A, et al. Gamma Knife stereotactic radiosurgery for cavernous sinus meningioma: long-term follow-up in 200 patients. *J Neurosurg*. 2019;130(6):1799–1808.
33. Sheehan JP, Starke RM, Kano H, et al. Gamma Knife radiosurgery for posterior fossa meningiomas: a multicenter study. *J Neurosurg*. 2015;122(6):1479–1489.
34. Starke R, Kano H, Ding D, et al. Stereotactic radiosurgery of petroclival meningiomas: a multicenter study. *J Neurooncol*. 2014;119(1):169–176.
35. Mehta GU, Zenonos G, Patibandla MR, et al. Outcomes of stereotactic radiosurgery for foramen magnum meningiomas: an international multicenter study. *J Neurosurg*. 2018;129(2): 383–389.
36. Cohen-Inbar O, Lee C-C, Sheehan JP. The contemporary role of stereotactic radiosurgery in the treatment of meningiomas. *Neurosurg Clin N Am*. 2016;27(2):215–228.
37. Kollová A, Liscák R, Novotný J Jr, et al. Gamma Knife surgery for benign meningioma. *J Neurosurg*. 2007;107(2): 325–336.
38. Cai R, Barnett GH, Novak E, et al. Principal risk of peritumoral edema after stereotactic radiosurgery for intracranial meningioma is tumor-brain contact interface area. *Neurosurgery*. 2010;66(3):513–522.
39. Unger KR, Lominska CE, Chanyasulkit J, et al. Risk factors for posttreatment edema in patients treated with stereotactic radiosurgery for meningiomas. *Neurosurgery*. 2012;70(3): 639–645.
40. Sheehan JP, Lee C-C, Xu Z, et al. Edema following Gamma Knife radiosurgery for parasagittal and parafalcine meningiomas. *J Neurosurg*. 2015;123(5):1287–1293.
41. Goldbrunner R, Minniti G, Preusser M, et al. EANO guidelines for the diagnosis and treatment of meningiomas. *Lancet Oncol*. 2016;17(9):e383–e391.
42. Islim AI, Mohan M, Moon RDC, et al. Incidental intracranial meningiomas: a systematic review and meta-analysis of prognostic factors and outcomes. *J Neurooncol*. 2019;142(2): 211–221.
43. Bunevicius A, Sheehan D, Vance ML, et al. Outcomes of Cushing's disease following Gamma Knife radiosurgery: effect of a center's growing experience and era of treatment. *J Neurosurg*. 2021;134(2):547–554.
44. Scaringi C, Minniti G, Bozzao A, et al. Radiation-induced malignant meningioma following proton beam therapy for a choroidal melanoma. *J Clin Neurosci*. 2015;22(6):1036–1037.

Disclosures

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