Stereotactic Radiosurgery for Atypical (World Health Organization II) and Anaplastic (World Health Organization III) Meningiomas: Results From a Multicenter, International Cohort Study

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BACKGROUND: Atypical and anaplastic meningiomas have reduced progression-free/overall survival (PFS/OS) compared to benign meningiomas. Stereotactic radiosurgery (SRS) for atypical meningiomas (AMs) and anaplastic meningiomas (malignant meningiomas, MMs) has not been adequately described.

OBJECTIVE: To define clinical/radiographic outcomes for patients undergoing SRS for AM/MMs.

METHODS: An international, multicenter, retrospective cohort study was performed to define clinical/imaging outcomes for patients receiving SRS for AM/MMs. Tumor progression was assessed with response assessment in neuro-oncology (RANO) criteria. Factors associated with PFS/OS were assessed using Kaplan-Meier analysis and a Cox proportional hazards model.

RESULTS: A total of 271 patients received SRS for AMs (n = 233, 85.9%) or MMs (n = 38, 14.0%). Single-fraction SRS was most commonly employed (n = 264, 97.4%) with a mean target dose of 14.8 Gy. SRS was used as adjuvant treatment (n = 85, 31.4%), salvage therapy (n = 182, 67.2%), or primary therapy (1.5%). The 5-yr PFS/OS rate was 33.6% and 77.0%, respectively. Increasing age (hazard ratio (HR) = 1.01, $P < .05$) and a Ki-67 index > 15% (HR = 1.66, $P < .03$) negatively correlated with PFS. MMs (HR = 3.21, $P < .05$), increased age (HR = 1.04, $P = .04$), and reduced KPS (HR = 0.95, $P = .04$) were associated with shortened OS. Adjuvant versus salvage SRS did not impact PFS/OS. A shortened interval between surgery and SRS improved PFS for AMs (HR = 0.99, $P = .02$) on subgroup analysis. Radiation necrosis occurred in 34 (12.5%) patients. Five-year rates of repeat surgery/radiation were 33.8% and 60.4%, respectively.

CONCLUSION: AM/MMs remain challenging tumors to treat. Elevated proliferative indices are associated with tumor recurrence, while MMs have worse survival. SRS can control AM/MMs in the short term, but the 5-yr PFS rates are low, underscoring the need for improved treatment options for these patients.

KEY WORDS: Meningioma, Atypical, Anaplastic, Gamma knife radiosurgery, Radiosurgery, Stereotactic

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Meningiomas are the most common benign intracranial neoplasms encountered in the United States, representing approximately one-third of central nervous system tumors.[1] The World Health Organization (WHO) recognizes that a subset of meningiomas (atypical meningiomas [AMs] and anaplastic meningiomas [herein referred to as malignant meningiomas, MMs]) have increased rates of recurrence and reduced overall survival (OS) following surgical resection.[2] Following gross total resection (GTR), 5-yr local control

ABBREVIATIONS: AM, atypical meningioma; **ARE,** adverse radiation event; **EBRT,** external beam radiotherapy; **GTR,** gross total resection; **HR,** hazard ratio; **IQR,** interquartile range; **MM,** malignant meningioma; **OS,** overall survival; **PFS,** progression-free survival; **RANO,** response assessment in neuro-oncology; **RTOG,** radiation therapy oncology group; **SRS,** stereotactic radiosurgery; **WHO,** World Health Organization

rates are 85% to 90% whereas in instances of incomplete resection, the 5-yr local control rates decrease to 50%.[3-5] How these patients are managed postoperatively remains controversial. Given the higher proliferative indices of AM/MMs, multimodality treatment including external beam radiotherapy (EBRT) or stereotactic radiosurgery (SRS) is often necessary to achieve tumor control.[6,7]

The major question currently in the management of AM/MMs is whether adjuvant radiation versus observation is advisable for patients with AM/MMs. This has largely been investigated in the context of EBRT.[8,9] While large series examining the outcomes of SRS for benign meningiomas have been reported, less data exist on the optimal radiosurgical strategies for patients with AM/MMs.[7,10-13] Many of these studies have been limited by small cohort sizes and many series have analyzed patients prior to the 2000 WHO revision.[6] The need to understand the role of radiosurgery for these challenging tumors is underscored by the lack of systemic treatment options and paucity of ongoing clinical trials available to patients with AM/MMs

We therefore performed an international, multicenter retrospective cohort study to define the impact of SRS on patients with AM/MMs who were diagnosed after 2000.

METHODS

Study Design

Patients were identified from participating centers in the International Radiosurgery Research Foundation. Institutional review board approval was obtained at each center. As the 2000 WHO diagnostic criteria for AM/MMs were considerably revised, patients were eligible for analysis if their tumor had histolopathologic diagnosis after the 2000 WHO revision.[14] Patients with less than 6 mo of clinical/radiographic follow-up were excluded.

Radiosurgical Technique

Patients underwent SRS as previously described.[15] Patients were treated with SRS using the Gamma Knife® (Elekta, Stockholm, Sweden) radiosurgery device available at each institution. Dose selection was at the discretion of the treating neurosurgeron, radiation oncologist, and radiation physicist. All patients provided written informed consent.

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Follow-up and Study Parameters

Radiographic and clinical data were retrospectively reviewed. Adjuvant SRS was defined as the use of SRS to treat the surgical bed or residual tumor shortly after resection. Salvage SRS was defined as the use of SRS to treat either recurrent tumor (salvage-recurrent) or progressive residual tumor (salvage-residual). In rare cases, SRS was classified as the primary treatment in a patient with multiple high-grade meningiomas where the target lesion had not been specifically resected.

Tumor volumes and maximal diameters were calculated at the time of SRS and at each subsequent radiographic follow-up visit. Tumor volumes were approximated using the formula: abc/2.[16] Tumor progression was defined per Response assessment in neuro-oncology (RANO) criteria.[17] Progression-free survival (PFS) was defined as the interval between SRS and RANO progression. Overall survival (OS) was defined as the interval between SRS and date of death. Tumor regression was defined as a 20% or more volumetric decrease in the size of the targeted meningioma.

Adverse radiation events (AREs) were defined as the development of radiation necrosis. Radiation necrosis was defined progressive volumetric expansion of the treated meningioma with concurrent peritumoral edema that resolved or notably improved over time.[18]

Statistical Analysis

Univariate analysis was performed using the *t*-test and chi-square analysis to compare 2 populations for continuous and categorical variables, respectively. PFS, OS, and AREs were assessed using a Cox hazards proportional regression model. A *P*-value less than .05 was deemed statistically significant. Factors with a *P*-value of .1 or less on univariate analysis were entered into a multivariate analysis to assess clinical variables associated with PFS, OS, and adverse events. Statistical analysis was performed using Prism (version 7.0b) and R (https://www.R-project.org, version 3.6.2).

RESULTS

Patient and Radiosurgical Characteristics

A total of 271 patients met inclusion criteria. Baseline characteristics of patients receiving SRS are summarized in Table 1. Most patients underwent SRS for AMs (AM = 233, 86.0%; MM = 38, 14.0%). SRS was used as adjuvant treatment in 85 patients (31.4%), salvage therapy for residual tumor in 41 individuals (15.1%), and salvage therapy for recurrent tumor in 141 patients (52.0%). Of the 85 patients who received adjuvant SRS, the majority (n = 73, 85.9%) had undergone subtotal resection. The median clinical/radiographic follow-up was 37.8 mo (interquartile range [IQR]: 21.7-65.3) and 36.2 mo (IQR: 21.2-63.4), respectively.

Four patients had SRS as the primary treatment of a newly identified tumor in a patient with a previous resection of an AM/MM. In these instances, an out-of-field, nodular recurrence was treated with SRS as primary therapy.

Radiosurgical parameters for patients are summarized in Table 2. The mean tumor volume targeted was 7.5 cm^3 (range: 0.1-54.5 cm^3) and was targeted with a mean of 14.8 Gy (range: 9.0-30.0 Gy) to the 50% isodose line. Single-fraction SRS was most commonly employed (97.4%, n = 264). The

TABLE 1. Baseline Demographics of Patients Receiving SRS for Atypical and Malignant Meningiomas

No. of patients	271
Age at SRS (yr)	59 ± 14.1
Female (n, %)	149 (54.9)
History of NF2	2 (0.7)
KPS at SRS	90 (80-90)
Symptoms at diagnosis	
Seizure	50 (18.5)
Headache	77 (28.4)
Focal neurological deficit	172 (63.4)
Incidental finding	25 (9.2)
Use of steroids at SRS	96 (35.4)
Use of AEDs at SRS	95 (35.1)
Meningioma location	
Convexity	91 (51.7)
Parasagittal/parafalcine	99 (36.5)
Skull base	79 (29.2)
Intraventricular	2 (0.7)
Presence of peritumoral edema	117 (43.2)
Indication for SRS	
Adjuvant treatment	85 (31.4)
Salvage therapy for residual tumor	41(15.1)
Salvage therapy for recurrent tumor	141 (52.0)
Primary treatment	4 (1.5)
Prior surgery (n, %)	267 (98.5)
No. prior surgeries[a]	1.5 ± 1.1
Interval between most recent surgery and SRS (mo)[a]	12.5 (4.4-32.7)
Gross total resection (n, %)	131 (49.1)
Subtotal resection (n, %)	136 (50.9)
Use of preoperative embolization (n, %)[a]	18 (6.7)
Pathology	
Atypical meningioma	233 (86.0)
Malignant meningioma	38 (14.0)
Presence of necrosis[b]	152 (65.0)
Ki-67 index[c]	15% (10%-20%)
Presence of brain invasion[d]	80 (36.0)
Presence of nuclear atypia[e]	81 (37.3)
Prior ionizing radiation (n, %)	70 (25.8)
SRS[f]	16 (22.9)
Fractioned RT	55 (78.6)
Prior radiation dose (Gy)[f]	47.7 ± 15.3
Interval between radiation and index SRS (mo)[f]	50.7 (28.9-73.8)
Clinical follow-up (mo)	37.8 (21.7-65.3)
Radiographic follow-up (mo)	36.2 (21.2-63.4)

AED, antiepileptics; EBRT, external beam radiotherapy; Gy, gray; IMRT, intensity-modulated radiation therapy; KPS, Karnofsky Performance Status; NF2, neurofibromatosis type 2; RT, radiation therapy; SRS, stereotactic radiosurgery.
Data represented as mean ± standard deviation, median (interquartile range) or n (%).
[a]Of 267 patients who underwent previous surgery.
[b]Data available for 234 patients.
[c]Data available for 176 patients.
[d]Data available for 222 patients.
[e]Data available for 217 patients.
[f]Of 70 patients who underwent prior radiation treatment.

TABLE 2. Meningioma Characteristics and Radiosurgical Parameters

Targeted meningioma volume (cm^3)	7.5 ± 8.6
Maximum targeted meningioma diameter (cm)	3.0 ± 2.7
Treatment volume (cm^3)	9.7 ± 12.0
Margin dose (Gy)	14.8 ± 2.3
Maximum dose (Gy)	28.4 ± 5.2
No. of isocenters	15.1 ± 9.4
Isodose (%)	50 (30-80)
No. of fractions	1 (1-5)

Gy, gray.
Data represented as mean ± SD, median (range).

mean treatment dose was similar for radiation-naive patients (14.8 Gy) and for patients who received prior radiation (15.0 Gy).

Progression-Free Survival

The median PFS following SRS was 37.5 mo for all patients. The actuarial PFS rates at 1, 2, and 5 yr were 83.1%, 66.6%, and 33.6%, respectively (Figure 1A). On univariate analysis, MMs, prior radiation therapy, a Ki-67 index > 15%, and an increased interval between surgery and SRS were associated with shorter PFS (Table 3). On multivariate analysis, increasing age (Hazard Ratio (HR) = 1.01 (95% CI 1.00-1.03), $P < .05$) and a Ki-67 index > 15% (HR = 1.66 (95% CI 1.05-2.62), $P < .03$) were associated with reduced PFS (Table 3, Figure 1B). For individuals with a Ki-67 index > 15%, the median PFS was 22.3 mo. In comparison, patients with a Ki-67 index ≤ 15% fared better with a median PFS of 43.8 mo (Figure 1B).

The median PFS for patients with MMs was 31.8 mo compared to 41.1 mo for individuals with AMs (univariate: HR = 3.7 (95% CI 2.1-6.7), $P < .01$). The 1, 2, and 5-yr PFS rates were 84.2%, 67.8%, and 36.4% for AMs and 76.3%, 59.9%, and 20.4% for MMs.

There was no difference in PFS with regards to the indication of SRS (adjuvant versus salvage SRS, Table 3). Decreased time to SRS following surgery was associated with a modest improvement in PFS on univariate analysis (HR = 0.99, (95% CI 0.98-0.99), $P < .01$), but this did not achieve statistical significance on multivariate analysis (HR = 0.99 (95% CI 0.98-1.00), $P = .05$). A shortened interval between surgery and SRS correlated with improved PFS for AMs (HR = 0.99 (95% CI 0.98-0.99) $P = .02$) on subgroup analysis.

Examining only individuals with residual tumor after surgery, there was no statistical difference in PFS between individuals treated with adjuvant SRS (PFS = 47.7 mo) versus salvage-residual SRS (PFS = 27.3 mo) (HR = 0.66 (95% CI 0.39-1.13); $P = 0.13$). Furthermore, there was no statistical difference in terms of PFS amongst individuals treated with SRS to the tumor bed following GTR (n = 12) compared to those who underwent salvage-recurrent SRS

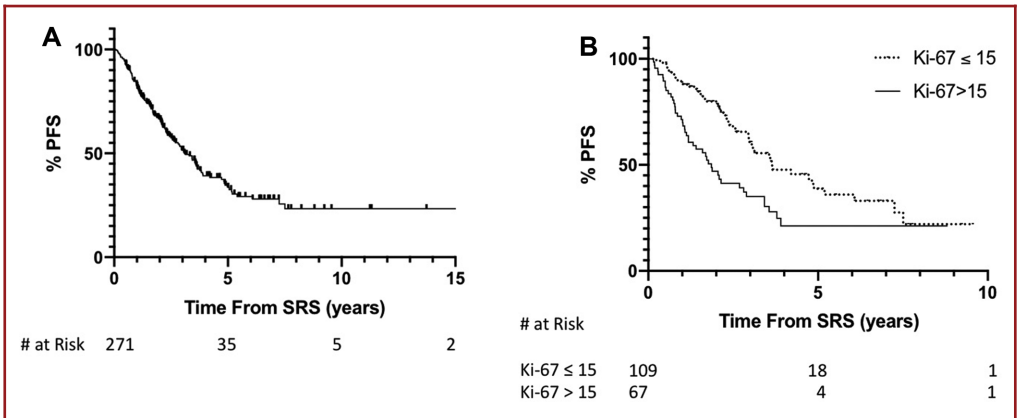

FIGURE 1. *Kaplan-Meier analysis of patients who received SRS for high-grade meningiomas.* **A**, *The actuarial tumor control rates at 1, 2, and 5 yr were 83.1%, 66.6%, and 33.6%, respectively.* **B**, *A Ki-67 index greater than 15% was associated with decreased PFS (HR 1.66 (95% CI 1.05-2.62), P < .03). For individuals with a Ki-67 index > 15, the median PFS was 22.3 mo with actuarial PFS rates of 69.9% and 47.0% at 1 and 2 yr, respectively. Those with a Ki-67 index ≤ 15 had a median PFS of 43.8 mo with actuarial tumor control rates of 88.8% and 79.9% at 1 and 2 yr, respectively.*

TABLE 3. Univariate and Multivariate Factors Associated With PFS

	Univariate		Multivariate	
	PFS HR (95% CI)	*P* value	PFS HR (95% CI)	*P* value
Age (yr)	1.01 (0.99-1.02)	.06	1.02 (1.00-1.03)	<.05
Gender	0.92 (0.66-1.26)	.59	–	–
KPS	0.99 (0.97-1.01)	.17	–	–
Indication for SRS				
Adjuvant treatment	Reference	n/a	–	–
Salvage therapy for residual tumor	1.7 (0.9-2.8)	.13	–	–
Salvage therapy for recurrent tumor	1.3 (0.9-1.9)	.34	–	–
Primary treatment	1.1 (0.3-4.8)	.91	–	–
Interval surgery and SRS	0.99 (0.98-0.99)	.01	0.99 (0.98-1.00)	.05
GTR at most recent surgery	1.12 (0.81-1.54)	.49	–	–
Tumor volume	1.02 (0.99-1.04)	.08	1.00 (0.97-1.02)	.84
Tumor location	0.87 (0.81-1.06)	.16	–	–
Presence of peritumoral edema[a]	1.14 (0.81-1.60)	.46	–	–
Preoperative tumor embolization[b]	1.53 (0.90-2.61)	.12	–	–
Malignant meningioma	1.58 (1.06-2.36)	.03	1.34 (0.79-2.28)	.28
Presence of necrosis on histology[c]	1.00 (0.69-1.43)	.99	–	–
Ki-67 > 15[d]	2.00 (1.31-2.97)	<.01	1.66 (1.05-2.62)	.03
Presence of Brain invasion[e]	1.13 (0.80-1.66)	.48	–	–
Histologic nuclear atypia[f]	0.89 (0.82-1.29)	.55	–	–
Prior radiation therapy	1.56 (1.11-2.20)	.01	1.61 (0.98-2.64)	.06
Margin radiosurgical dose > 16 Gy	1.11 (0.79-1.58)	.55	–	–
Maximum radiosurgical dose (Gy)	1.00 (0.97-1.04)	.78	–	–

GTR, gross total resection; Gy, gray; KPS, Karnofsky Performance Status; PFS, progression-free survival; SRS, stereotactic radiosurgery.
[a]Data from 255 patients.
[b]Data from 268 patients.
[c]Data available for 234 patients.
[d]Data available for 176 patients.
[e]Data available for 222 patients.
[f]Data available for 217 patients.

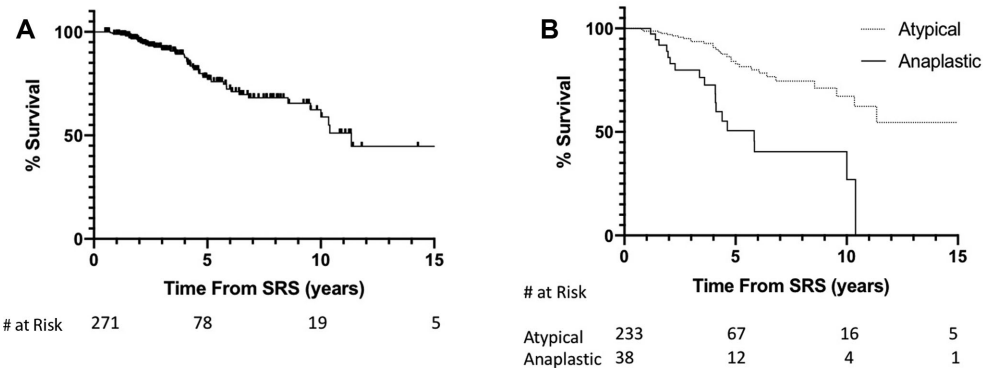

FIGURE 2. **A**, *The median overall survival following SRS was 136.2 mo with 2, 5, and 10-yr survivorship rates of 95.3%, 77.0%, and 62.4%, respectively.* **B**, *MMs had a decreased median OS compared to AMs (MMs OS: 70.0; AMs OS: 187.4 mo; HR 3.21 (95% CI 1.02-10.05), P < .05). The 5-yr actuarial OS rate for MMs was 50.6% compared to 82.9% for AMs.*

(HR = 0.52 (95% CI 0.24-1.10), P = .09). There was likewise no benefit to adjuvant SRS to the tumor bed compared to adjuvant SRS to nodular tumor (HR = 0.53 (95% CI 0.22-1.26), P = .15).

Overall Survival

The median OS following SRS was 136.2 mo with 2, 5, and 10-yr survivorship rates of 95.3%, 77.0%, and 62.4%, respectively (Figure 2A). On multivariate analysis, increasing age (HR = 1.04 (95% CI 1.00-1.08), P = .04), reduced KPS (HR = 0.95 (95% CI 0.91-0.99), P = .04), and malignant pathology (HR = 3.21 (95% CI 1.02-10.05, P < .05) negatively correlated with OS (Table 4). Elevated Ki-67, while associated with shortened PFS, was not associated with reduced OS on multivariate analysis.

The median OS for MMs in this study was 70.0 mo compared to 187.4 mo for AMs (P = .03, Figure 2B). The 2, 5, and 10-yr actuarial OS rates for MMs were 86.0%, 50.6%, and 40.5%, respectively. For AMs, 97.0%, 82.9%, and 67.2% of patients were alive at 2, 5, and 10 yr following SRS.

The indication for SRS had no appreciable influence on OS (Table 4). When examining patients with residual tumor, there was a trend toward improved OS in individuals who received adjuvant SRS but this was not significant (HR = 0.51 (95% CI 0.23-1.17), P = .09). Similarly, there was no statistical significance in OS between the 2 cohorts when survivorship was measured after the most recent resection (HR = 0.55 (95% CI 0.24-1.27), P = .15). Likewise, no difference in OS was observed when comparing patients with GTR treated with adjuvant SRS versus salvage SRS when measured from the time of SRS (HR = 0.56 (95% CI 0.13-2.32), P = .63) or from the time of last resection (HR = 0.59 (95% CI 0.14-2.47), P = .49).

Tumor Response

Most AM/MMs did not regress (66.4%) following SRS. Of those that did, the median time to tumor regression was 93.8 mo (Figure 3A). Over the course of follow-up, 140 (51.7%) patients had progressive disease. Of those patients with progressive disease, 25 (17.8%) patients initially had tumor regression.

AREs and Further Management

AREs occurred in 34 patients (12.5%) of which 17 cases (6.3%) were symptomatic. Of the symptomatic cases, 6 (35.3%) were treated with steroids, 6 (35.3%) received bevacizumab, and 3 individuals (17.6%) required surgery. The ARE rates were 9.4%, 11.0%, and 12.3% at 1, 2, and 3 yr following SRS, respectively (Figure 3B). On multivariate analysis, increasing age was associated with increased ARE development (HR = 1.04 (95% CI 1.00-1.08), P = .04, Table 5).

A total of 120 patients (44.3%) underwent further radiation (SRS = 103 (85.8%), EBRT = 35 (29.2%), proton beam = 3 (2.5%)) with a median time to subsequent radiation delivery of 45.9 mo (Figure 3C). Fifty-seven patients (21.0%) underwent subsequent meningioma resection with a median time to further surgery of 110.8 mo (Figure 3D).

DISCUSSION

AM/MMs remain challenging tumors to treat despite advances in multimodality management.[3,5,19] SRS is well recognized in the treatment of benign meningiomas, but its application for AM/MMs has been less well defined.[10,15] Until now, data examining outcomes for AM/MMs have been derived from small case series.[3,5,7,12,13,20]

Previously, the largest series reporting on SRS for high-grade meningiomas was by Pollock et al who described the outcomes of 50 patients treated with SRS.[21] Similar to this study, the 5-yr PFS/OS rates were 40.0% and 62.0%, respectively.[21] Tumor control rates have been variable for high-grade meningiomas treated with SRS with 5-yr PFS rates ranging between 16% and 83%.[7,12,22] This variability is likely attributable to small case series, the inclusion of meningiomas diagnosed prior to 2000,

TABLE 4. Univariate and Multivariate Factors Associated With OS

	Univariate		Multivariate	
	OS HR (95% CI)	*P* value	OS HR (95% CI)	*P* value
Age	1.04 (1.02-1.06)	<.01	1.04 (1.00-1.08)	.04
Gender	1.09 (0.61-1.93)	.78	–	–
KPS	0.97 (0.94-0.99)	.03	0.95 (0.91-0.99)	.04
Indication for SRS				
Adjuvant treatment	Reference	n/a	–	–
Salvage therapy for residual tumor	2.5 (1.0-5.9)	.36	–	–
Salvage therapy for recurrent tumor	1.3 (0.7-2.7)	.81	–	–
Primary treatment	1.0 (0.1-7.3)	.98	–	–
Interval surgery and SRS	1.00 (0.99-1.01)	.89	–	–
GTR at most recent surgery	1.18 (0.70-2.09)	.57	–	–
Tumor volume	1.01 (0.97-1.05)	.61	–	–
Tumor location	0.96 (0.67-1.34)	.81	–	–
Presence of peritumoral edema[a]	1.46 (0.81-2.62)	.21	–	–
Preoperative tumor embolization[b]	1.78 (0.80-3.98)	.16	–	–
Malignant meningioma	3.72 (2.06-6.72)	<.01	3.21 (1.02-10.05)	<.05
Presence of necrosis on histology[c]	1.49 (0.75-2.97)	.25	–	–
Ki-67 > 15[d]	2.82 (1.34-5.91)	<.01	0.90 (0.36-2.50)	.90
Presence of Brain invasion[e]	0.78 (0.39-1.57)	.48	–	–
Histologic nuclear atypia[f]	0.65 (0.32-1.28)	.21	–	–
Prior radiation therapy	2.47 (1.39-4.39)	<.01	1.8 (0.64-5.15)	.27
Margin radiosurgical dose > 16 Gy	1.31 (0.71-2.42)	.39	–	–
Maximum radiosurgical dose (Gy)	1.02 (0.97-1.08)	.39	–	–

GTR, gross total resection; Gy, gray; KPS, Karnofsky Performance Status; OS, overall survival; SRS, stereotactic radiosurgery.
[a]Data from 255 patients.
[b]Data from 268 patients.
[c]Data available for 234 patients.
[d]Data available for 176 patients.
[e]Data available for 222 patients.
[f]Data available for 217 patients.

and differences in how meningiomas were treated before receiving SRS.[6]

In a prospective trial, the radiation therapy oncology group (RTOG) found that the 3-yr PFS rate following radiation therapy was 58.0% for high-risk meningiomas (MMs, recurrent/subtotally resected AMs).[9] Our data are similar to this with a 3-yr PFS rate of 51.0%. The local control rate in the high-risk RTOG study was 69% with 40% patients treated for MMs[9] In their study, the RTOG treated high-risk meningiomas with 60 Gy, potentially explaining the high local control rate. It is possible that higher margin doses administered with SRS can improve PFS/OS. Prior studies note that AMs improved PFS when treated with greater than 60 Gy via proton therapy.[23] The mean dose used in this study was 14.8 Gy, with only 38 patients (14.0%) receiving greater than 16 Gy. Thus, dose escalation, potentially in a hypofractionated manner, may improve PFS for patients with AM/MMs via SRS and warrants further investigation.

Elevated proliferative indices rather than tumor grade were associated with shorter PFS. Pollock et al found that tumor grade was not associated with PFS, and other authors have suggested that elevated proliferative indices may lead to earlier tumor progression.[21,24,25] Here, MMs were associated with a significant reduction in OS. Thus, it seems that elevated proliferative indices may be a major driver of early tumor recurrence for AM/MMs, but tumor grade may play an important role in determining whether recurrent tumors are responsive to subsequent treatments. Older age and reduced KPS were similarly poor prognostic factors with regards to OS, which is consistent with prior reports.[12,25,26]

The optimal timing of radiosurgery and/or radiotherapy for AM/MMs remains the subject of ongoing debate.[5,11,19,27,28] Most of the literature has specifically examined the use of EBRT for AMs. Several studies suggest the use of adjuvant EBRT following subtotal resection of AMs improves tumor control,[4,19,27,29] although this has not been a consistent finding.[5] Following GTR, most studies report little benefit in utilizing adjuvant EBRT, although this remains controversial and is currently being addressed in an ongoing prospective, randomized controlled trial.[28] Our data did not show improvement in PFS when comparing adjuvant SRS directed towards the surgical bed versus residual tumor. Only 12 individuals received adjuvant SRS

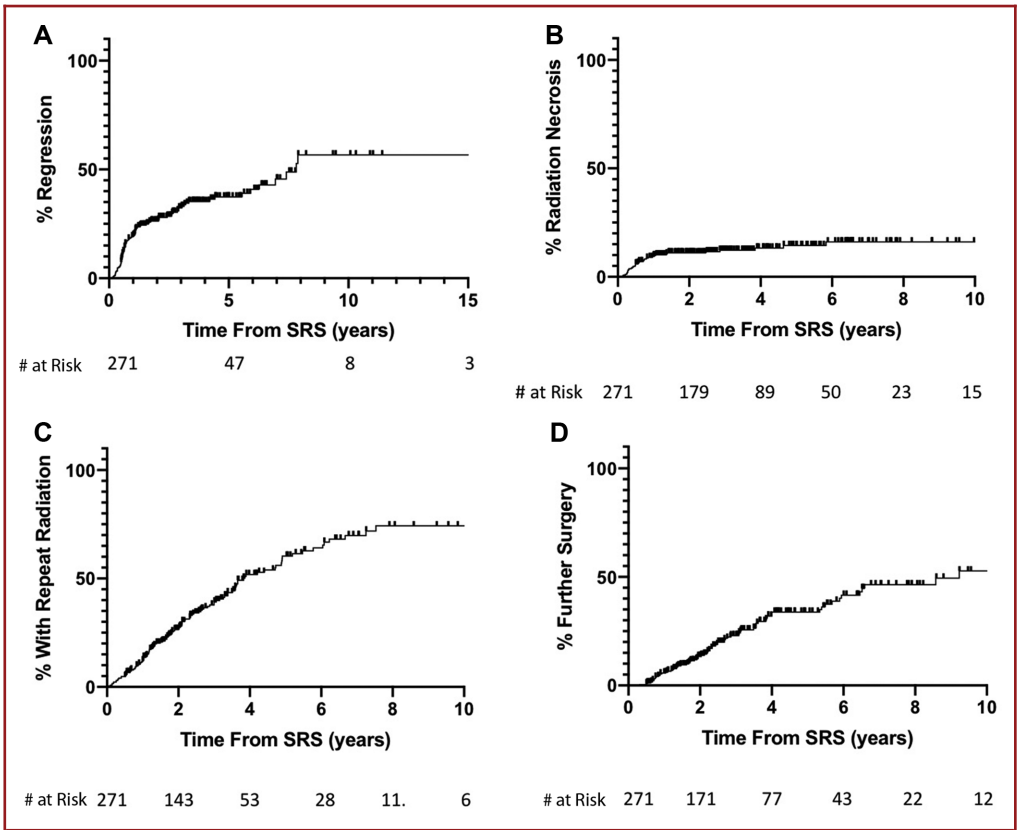

FIGURE 3. **A**, *The 1, 2, and 5-yr tumor regression rates were 19.2%, 26.3%, and 37.4%, respectively.* **B**, *AREs occurred in 34 (12.5%) patients. The ARE rates were 9.4%, 11.0%, and 12.3% at 1, 2, and 3 yr following SRS, respectively.* **C**, *Subsequent radiation occurred in 120 patients (44.3%). Approximately 51.9% patients underwent further radiation 4 yr after SRS.* **D**, *Fifty-seven patients underwent subsequent surgery. The actuarial rates of requiring further surgery were 5.7%, 13.4%, and 32.8% at 1, 2, and 4 yr following SRS, respectively.*

to the tumor bed; thus, our study is underpowered to detect subtle improvements for empiric adjuvant SRS without appreciable tumor.

Shorter durations between surgery and SRS were associated with improved PFS; however, this was not significant on multivariate analysis. AM/MM are unlikely to be cured by resection alone; thus, earlier treatment with SRS when the tumor is smaller and more distance remains between the target volume and critical structures may afford a more optimal dose delivery and more effective tumor control.

Our study did not identify adjuvant SRS as statistically superior to salvage SRS in terms of PFS/OS although there was a trend to this effect (47.7 mo versus 27.3 mo). In this study PFS was defined after SRS and is thus subject to lead time bias. A better comparison to assess the efficacy of adjuvant SRS would be to compare patients receiving SRS after resection with those who underwent observation. As many patients underwent resection at other institutions and were referred for SRS at the time of tumor progression, we were not able to precisely identify the time of first tumor progression following surgery. We are thus limited in our ability to assess whether adjuvant SRS may afford substantial tumor control following initial resection. Further studies will be needed to clarify subgroups of high-grade meningioma patients who most benefit from adjuvant SRS.

Overall, most patients tolerated SRS well. Only 6.3% of patients developed symptomatic AREs and 5.5% required treatment. A complication rate between 3% and 62% following radiosurgery for high-grade meningiomas has been previously reported.[7] The rate of AREs appears to be higher in patients with AM/MMs compared to patients receiving SRS for benign meningiomas.[10] The reasons for this in the current series may be related to multiple prior surgeries, prior radiation therapy, regional brain invasion, and the high incidence of baseline peritumoral edema.

Study Limitations

Our study has limitations which may be attributed to selection, reporting, and recall bias. The timing/indication of SRS was not standardized and was at the discretion of the treating

TABLE 5. Univariate and Multivariate Factors Associated With AREs

	Univariate		Multivariate	
	ARE HR (95% CI)	*P* value	ARE HR (95% CI)	*P* value
Age	1.03 (1.005-1.06)	.02	1.04 (1.00-1.08)	.04
Gender	1.43 (0.71-2.86)	.31	–	–
KPS	1.002 (0.97-1.04)	.91	–	–
Indication for SRS				
Adjuvant treatment	Reference	n/a	–	–
Salvage therapy for residual tumor	1.0 (0.3-3.5)	.88	–	–
Salvage therapy for recurrent tumor	1.9 (0.9-3.8)	.41	–	–
Primary treatment	5.8 (0.3-130.8)	.29	–	–
Interval surgery and SRS	0.99 (0.98- 1.00)	.27	–	–
GTR at most recent surgery	1.96 (0.95-4.04)	.06	1.63 (0.65-4.06)	.28
Tumor volume	1.01 (0.96-1.05)	.73	–	–
Tumor location	1.03 (0.64-1.65)	.89	–	–
Presence of peritumoral edema[a]	1.05 (0.50-2.21)	.88	–	–
Preoperative tumor embolization[b]	0.41 (0.05-3.09)	.39	–	–
Malignant meningioma	1.79 (0.75-4.22)	.18	–	–
Presence of necrosis on histology[c]	1.39 (0.58-3.33)	.44	–	–
Ki-67 > 15[d]	1.01 (0.41-2.46)	.97	–	–
Presence of brain invasion[e]	1.01 (0.44-2.33)	.96	–	–
Histologic nuclear atypia[f]	0.49 (0.22-1.05)	.06	0.9 (0.3-2.64)	.84
Prior radiation therapy	0.44 (0.20-0.98)	.04	0.42 (0.15-1.17)	.1
Maximum radiosurgical dose > 32 Gy	0.41 (0.19-0.87)	.02	0.59 (0.18-1.94)	.39

ARE, adverse radiation event; GTR, gross total resection; Gy, gray; KPS, Karnofsky Performance Status; SRS, stereotactic radiosurgery.
[a]Data from 255 patients.
[b]Data from 268 patients.
[c]Data available for 234 patients.
[d]Data available for 176 patients.
[e]Data available for 222 patients.
[f]Data available for 217 patients.

neurosurgeon. Many patients received prior radiation and multiple surgical interventions. These patients invariably have later stage disease and may respond differently to SRS than radiation-naïve patients. We were also not able to reliably document whether tumor progression occurred in or out of the radiosurgical field. Further work will need to be done to detail this important aspect of meningioma failure following SRS.

CONCLUSION

This manuscript represents the largest series of high-grade meningiomas treated with SRS. Elevated proliferative indices are a major driver of tumor recurrence, while higher tumor grade is associated with decreased OS. SRS is effective at controlling AM/MMs for several years, but recurrence rates are not inconsequential and further multimodality care is often required to achieve tumor control.

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