Gamma Knife radiosurgery of large skull base meningiomas

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OBJECT Stereotactic radiosurgery (SRS) has become a common treatment modality for intracranial meningiomas. Skull base meningiomas greater than 8 cm³ in volume have been found to have worse outcomes following SRS. When symptomatic, patients with these tumors are often initially treated with resection. For tumors located in close proximity to eloquent structures or in patients unwilling or unable to undergo a resection, SRS may be an acceptable therapeutic approach. In this study, the authors review the SRS outcomes of skull base meningiomas greater than 8 cm³ in volume, which corresponds to a lesion with an approximate diameter of 2.5 cm.

METHODS The authors reviewed the data in a prospectively compiled database documenting the outcomes of 469 patients with skull base meningiomas treated with single-session Gamma Knife radiosurgery (GKRS). Seventy-five patients had tumors greater than 8 cm³ in volume, which was defined as a large tumor. All patients had a minimum follow-up of 6 months, but patients were included if they had a complication at any time point. Thirty patients were treated with upfront GKRS, and 45 were treated following microsurgery. Patient and tumor characteristics were assessed to determine predictors of new or worsening neurological function and tumor progression following GKRS.

RESULTS After a mean follow-up of 6.5 years (range 0.5–21 years), the tumor volume was unchanged in 37 patients (49%), decreased in 26 patients (35%), and increased in 12 patients (16%). Actuarial rates of progression-free survival at 3, 5, and 10 years were 90.3%, 88.6%, and 77.2%, respectively. Four patients had new or worsened edema following GKRS, but preexisting edema decreased in 3 patients. In Cox multivariable analysis, covariates associated with tumor progression were 1) presentation with any cranial nerve (CN) deficit from III to VI (hazard ratio [HR] 3.78, 95% CI 1.91–7.45; $p < 0.001$), history of radiotherapy (HR 12.06, 95% CI 2.04–71.27; $p = 0.006$), and tumor volume greater than 14 cm³ (HR 6.86, 95% CI 0.88–53.36; $p = 0.066$). In those patients with detailed clinical follow-up ($n = 64$), neurological function was unchanged in 37 patients (58%), improved in 16 patients (25%), and deteriorated in 11 patients (17%). In multivariate analysis, the factors predictive of new or worsening neurological function were history of surgery (OR 3.00, 95% CI 1.13–7.95; $p = 0.027$), presentation with any CN deficit from III to VI (OR 3.94, 95% CI 1.49–10.24; $p = 0.007$), and decreasing maximal dose (OR 0.76, 95% CI 0.63–0.93; $p = 0.007$). Tumor progression was present in 64% of patients with new or worsening neurological decline.

CONCLUSIONS Stereotactic radiosurgery affords a reasonable rate of tumor control for large skull base meningiomas and does so with a low incidence of neurological deficits. Those with a tumor less than 14 cm³ in volume and without presenting CN deficit from III to VI were more likely to have effective tumor control.

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KEY WORDS stereotactic radiosurgery; Gamma Knife radiosurgery; meningioma; skull base; outcome; recurrence; microsurgery

MENINGIOMAS are the most frequently reported primary intracranial neoplasms in the US. Most of these lesions are benign (i.e., WHO Grade I) with a low tendency for invasion and recurrence and

a natural history of slow growth. Within the intracranial space, there is a narrow capacity for mass expansion. The primary approach for large meningiomas has been resection. Despite a dramatic decline in surgical morbidity for

ABBREVIATIONS CN = cranial nerve; CPA = cerebellopontine angle; GKRS = Gamma Knife radiosurgery; HR = hazard ratio; SRS = stereotactic radiosurgery.

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meningiomas reported over the last 2 decades, gross-total resection of meningiomas in critical locations, especially the skull base, has remained a challenge, and patients often require multiple surgeries leading to increased morbidity and mortality.^{6,10,36} In recent years, primary or adjuvant treatment with stereotactic radiosurgery (SRS) has gained favor. SRS has demonstrated its safety and efficacy in the control of benign tumors, particularly for small to moderately sized meningiomas. Tumor control rates for WHO Grade I skull base meningiomas after SRS average approximately 91% and 88% at 5 and 10 years, respectively.^{13,19,22,27,33–35,38,39,48,51}

Most meningioma radiosurgical series have excluded large volume tumors. Traditionally, a tumor diameter of 30–35 mm was the recommended cutoff for radiosurgery.^{30–32} In prior studies, large meningiomas have been treated with varying degrees of success, but radiosurgery outcomes appear to worsen for patients harboring meningiomas greater than 8 cm³ in volume.^{8,15,16,20,42} An 8-cm³ volume corresponds to a lesion with an approximate diameter of 2.5 cm. Radiosurgery to lesions in excess of 8-cm³ volume has been linked to worsening outcome with arteriovenous malformations, acoustic neuromas, and brain metastases as well.^{12,18,26} In the present study, we retrospectively reviewed data of patients harboring large WHO Grade I skull base meningiomas (volume > 8 cm³) who were treated with single-session Gamma Knife radiosurgery (GKRS) to identify prognostic factors associated with successful and adverse radiological and clinical outcomes.

Methods

Patient Population

This is a retrospective analysis of a prospectively maintained database approved by the University of Virginia institutional review board. The database was assessed from 1989 to 2013 for patients with skull base meningiomas treated with single-session GKRS at the University of Virginia (n = 469). The diagnosis was confirmed either by tissue pathology or characteristic findings for meningiomas on neuroimaging studies. Tumors typically exhibited radiological features of a meningioma including dural base, extraaxial location, uniform contrast enhancement, and intratumoral calcification. Exclusion criteria included patients with multiple meningiomas, history of prior cancer, follow-up less than 6 months unless there was a complication, and a confirmed tumor histological grade greater than WHO Grade I. All patients with tumor progression and all those with complications following GKRS were included, regardless of follow-up duration. Consequently, 75 patients had large tumors (> 8 cm³) as assessed with tumor volumetry using radiosurgical planning software at the time of GKRS and were included for analysis.

Patients were considered for GKRS if they were not disabled by their tumor, i.e., Karnofsky Performance Scale score < 70. For those who underwent upfront treatment with GKRS, patients were not candidates for primary resection based upon their advanced age, the projected operative risks based on medical comorbidities, and/or refusal of microsurgical resection. Adjuvant radiosurgery was

performed in patients with recurrence of lesions following microsurgical excision or as part of multimodality treatment whereby the risks of surgical gross-total resection outweighed the benefits of multimodality therapy.

Patient and Tumor Attributes

Of the 75 patients with large skull base meningiomas, 51 were female (68%) and 24 were male (32%), with a median age of 55 years (range 19–85 years). Forty-five patients (60%) had a history of surgery and histologically confirmed WHO Grade I meningiomas, while the remaining 30 patients treated with upfront radiosurgery had neuroimaging characteristics and a clinical history consistent with a benign meningioma (40%). Alteration in function of cranial nerves (CNs) III, IV, V, or VI was the most common neurological deficit on presentation. The mean volume of tumors prior to radiosurgery was 14.1 ± 6.7 cm³ (median 12.4 cm³, range 8.1–54.8 cm³). The parasellar region (n = 42, 56%) and cerebellopontine angle (CPA) (n = 10, 13%) were the most common tumor locations. Preoperative patient characteristics, presentations, and tumor characteristics are detailed in Table 1.

Radiosurgical Technique

Our radiosurgical technique has been previously described.⁴⁹ In brief, patients underwent placement of a stereotactic Leksell model G stereotactic frame (Elekta Instruments Inc.) in the operating room. During frame placement, they received monitored anesthesia administered by an anesthesiologist. Stereotactic MRI was then obtained for the treatment planning. Pre- and postcontrast thin-slice (1-mm) volume acquisition axial and coronal MRI sequences were obtained. When an MRI was not able to be obtained due to medical contraindications (e.g., a cardiac pacemaker), a thin-slice stereotactic CT scan was obtained with and without contrast administration. Radiosurgical dose plans were formulated under the direction of a neurosurgeon in conjunction with a medical physicist and radiation oncologist. In general, the maximum dose to the optic apparatus was kept to 8 Gy or less. The Leksell Gamma Unit Model U was used until July 2001 when the C model (Elekta Instruments, Inc.) was instituted. The Gamma Knife Perfexion unit has been used to treat patients since 2007. The Kula software was used for dose planning from 1990 to June 1994, and then subsequently Elekta's Gamma Plan software was used. All patients in this series were treated with single-session radiosurgery. Initial tumor volume was assessed by contouring and then using Gamma Plan software.

Gamma Knife Radiosurgery Parameters

The mean dose to the tumor margin was 13.5 ± 3.5 Gy (range 4.8–30 Gy) with a mean maximal dose of 31 ± 5 Gy (range 23–40 Gy). Only 1 patient received a marginal dose of less than 9 Gy, and the 5th to 95th percentiles for marginal dose ranged from 9 to 20 Gy. The majority of tumors were treated with multiple isocenters (mean 13 ± 10 isocenters, range 1–43 isocenters) to the mean prescription isodose line of 42% ± 9% (range 30%–55%). Radiosurgery parameters are detailed in Table 2.

TABLE 1. Baseline characteristics of 75 patients with large skull base meningiomas treated with GKRS

Characteristic	Value (%)
Females	51 (68)
Age (yrs)	
Median $\pm$ SD	55 $\pm$ 13
Range	19–85
Previous resection	45 (60)
Previous radiotherapy	4 (5)
Previous GKRS	3 (4)
Initial presentation*	
Headache	18 (28)
Subjective dizziness	14 (22)
Seizure	3 (5)
CN	
III/IV/VI	29 (45)
V	33 (52)
VII	9 (14)
VIII	11 (17)
IX/X	1 (2)
XI	0 (0)
XII	1 (2)
Hypopituitarism	2 (3)
Body weakness	4 (6)
Dysgraphia	2 (3)
Cognition	1 (2)
Location	
Parasellar	42 (56)
Petroclival	9 (12)
Clival	6 (8)
Tentorial	3 (4)
CPA	10 (13)
Petrous	2 (3)
Sphenoidal	2 (3)
Jugular foramen	1 (1)
Tumor volume (cm ³)	
Mean $\pm$ SD	14.1 $\pm$ 6.7
Range	8.1–54.8
Tumor diameter (cm)	
Mean maximum	3.8 $\pm$ 0.8
Range	2.5–6
Edema on pre-GKRS imaging	4 (5)

* Clinical presentation data available for 64 patients.

Clinical and Radiological Follow-Up

Patients were routinely followed clinically and radiologically every 6 months for the first year, annually until 5 years after radiosurgery, and then every 2 years thereafter. At each follow-up visit, a neurological examination was performed to evaluate for new neurological deficits, and neuroimaging studies were reviewed to assess tumor response by both a neurosurgeon and neuroradiologist. All

TABLE 2. GKRS treatment parameters

Characteristic	Mean $\pm$ SD (range)
Margin dose (Gy)	13.5 $\pm$ 3.5 (4.8–30)
Maximum dose (Gy)	31 $\pm$ 5 (23–40)
Isodose line (%)	42 $\pm$ 9 (30–55)
No. of isocenters	13 $\pm$ 10 (1–43)

follow-up evaluation was performed at the University of Virginia, unless the patient was unable to travel to our institution. In such cases, the referring physician performed the follow-up and provided documentation of the patient's neurological status, as well as follow-up imaging.

All neuroimaging studies were reviewed by a neurosurgeon and a neuroradiologist at the University of Virginia. Lesions were categorized into the following locations defined by the presumed origin of maximal volume: sellar or parasellar, CPA, petrous, clival, petroclival, jugular foramen, and sphenoid.^{2,3,5,50,54,55} Petroclival meningiomas were defined as tumors whose maximal volume was centered over the region between the petrous apex and the upper two-thirds of the clivus.^{3,50} All parasellar lesions were in close proximity to the sella with cavernous sinus invasion.⁵⁴

Imaging outcome was determined by the last available radiological examination by a neurosurgeon and a neuroradiologist.⁴⁷ A decrease or increase in tumor size was defined as a 15% or greater change in tumor volume as compared with the volume at the time of GKRS.⁴⁷ Tumors with less than a 15% change from their initial volume were considered radiologically stable. Any patient with tumor progression of greater than 15% was considered a treatment failure even if this stabilized with further GKRS or surgery.⁴⁷ To make the determination of tumor volume, the tumor was outlined on radiological images and serial volumetric calculations were performed using Image J in all patient imaging studies (NIH).⁴⁷ The presence of perilesional edema was defined as FLAIR or T2-weighted changes around the tumor. These changes were evaluated by a neuroradiologist (M.S.) who assessed the radiosurgical planning MR images and the follow-up MR images for the presence of baseline edema and an exacerbation of the same after radiosurgery.

Statistical Analysis

Data are presented as median or mean and range for continuous variables, and as frequency and percentage for categorical variables. Calculations of normality were performed by ladder of powers and assessed graphically. Statistical analyses of categorical variables were conducted using chi-square, Fisher's exact, and Mantel-Haenszel tests for linear association as appropriate. Statistics of means were performed using an unpaired Student t-test, both with and without equal variance (Levene's test) as necessary and Wilcoxon rank-sum tests when variables were not normally distributed. The following dependent variables were assessed in univariate and multivariate analysis: tumor-free progression, worsening or new de-

cline in neurological function, and favorable outcome (no tumor progression or worsening or new decline in neurological function). Kaplan-Meier risk of tumor progression was calculated. Factors predictive of tumor progression ($p < 0.20$)⁴ were entered into multivariate Cox regression analysis to assess hazard ratios (HRs). Clinical covariates predicting new or worsening decline in neurological function with a univariate p value < 0.20 were included in multivariable logistic regression analysis. Additionally, clinical covariates predicting unfavorable outcome with a univariate p value < 0.20 were included in multivariable logistic regression analysis. Clinically significant variables and interaction expansion covariates were further assessed in both Cox and logistic multivariable analysis as deemed relevant. Youden indices were calculated to determine cutoffs for the dichotomized continuous variable tumor volume that yielded the optimal discrimination of tumor progression and overall outcome. Those p values ≤ 0.05 were considered statistically significant.

Results

Clinical Outcomes

Detailed clinical follow-up data were available for 64 patients. Neurological function was unchanged in 37 patients (58%), improved in 16 patients (25%), and declined in 11 patients (17%). Specific alterations in neurological function are displayed in Table 3. The most common CNs

to have new or worsening function following GKRS were II, III, and V, which each occurred in 4 patients (6%). Additionally, the most likely CNs to demonstrate improvement following GKRS were III, V, and VII occurring in 3 (5%), 4 (6%), and 3 (5%) of patients, respectively. In the current series, there was no evidence of vascular injury or brainstem ischemia as a result of SRS.

Predictors of new or worsening decline in neurological function in univariate analysis are demonstrated in Table 4. In multivariate analysis, the factors predictive of new or worsening decline in neurological function were history of surgery (OR = 3.00, 95% CI 1.13–7.95; $p = 0.027$), presentation with any CN deficit from III to VI (OR = 3.94, 95% CI 1.49–10.24; $p = 0.007$), and decreasing maximal dose (OR = 0.76, 95% CI 0.63–0.93; $p = 0.007$). Tumor progression was present in 7 (64%) of 11 patients with new or worsening decline in neurological function.

Radiological Outcome

The mean follow-up duration was 6.5 years (range 0.5–21 years). During this time, 37 patients (49%) displayed no change in tumor volume, 26 (35%) had decreased volume, and 12 (16%) displayed increased volume. Kaplan-Meier analysis demonstrated radiological progression-free survival at 3, 5, and 10 years to be 90.3%, 88.6%, and 77.2%, respectively (Fig. 1).

Four patients had a history of edema prior to SRS (5.3%). Following radiosurgery, 4 patients had new or

TABLE 3. Neurological outcomes for 64 patients with large skull base meningiomas treated with GKRS

Variable	Deficit Before GKRS	Stable Deficit	Improved Deficit	Worsened or New Deficit
Total patients (%)	59 (92)*	37 (58)†	16 (25)	11 (17)
Total no. of deficits per patient (%)				
Dizziness	14 (22)	12 (19)	2 (3)	0
Body weakness	4 (6)	3 (5)	1 (2)	0
Seizure	3 (5)	3 (5)	0	1 (2)
Hypopituitarism	2 (3)	2 (3)	0	0
Dysgraphia	2 (3)	2 (3)	0	0
Cognition	1 (2)	0	1 (2)	1 (2)
CN deficit*	52 (81)	33 (52)	12 (19)	9 (14)
CN I	2 (3)	2 (3)	0	0
CN II	19 (30)	15 (23)	1 (2)	4 (6)
CN III	24 (38)	18 (28)	3 (5)	4 (6)
CN IV	3 (5)	3 (5)	0	1 (2)
CN V	33 (52)	26 (41)	4 (6)	4 (6)
CN VI	16 (25)	16 (25)	0	1 (2)
CN VII	9 (14)	6 (9)	3 (5)	0
CN VIII	11 (17)	10 (16)	1 (2)	0
CN IX	0	0	0	0
CN X	1 (2)	0	1 (2)	0
CN XI	0	0	0	0
CN XII	1 (2)	1 (2)	0	0

* Some patients had multiple deficits

† Includes patients who did not present with a deficit.

TABLE 4. Predictors of new or worsening neurological deficits

Predictive Factor	OR	95% CI	p Value
Univariate analysis*			
Location			
All other locations	1.00		
Parasellar/pteroclival	7.10	0.85–59.54	0.071
History of radiotherapy	6.25	1.07–36.54	0.042
History of surgery	2.40	1.08–5.34	0.032
Any CN deficit from III to VI	2.98	1.43–6.23	0.004
Seizure	11.56	0.95–141.13	0.055
Increasing volume	1.06	0.98–1.15	0.171
Decreasing peripheral dose	0.82	0.64–1.05	0.118
Decreasing maximal dose	0.83	0.71–0.96	0.012
Multivariate analysis			
History of surgery	3.00	1.13–7.95	0.027
Any CN deficit from III to VI	3.94	1.49–10.24	0.007
Decreasing maximal dose	0.76	0.63–0.93	0.007

* Factors predictive of new/worsening symptoms ($p < 0.20$).

worsening edema within 18 months of treatment: 1 patient had progression of preexisting edema and 3 patients developed edema following SRS. The edema improved in 1 patient following a short course of steroids but persisted in the other 3 patients. Three patients with preexisting edema experienced improvement in the edema following radiosurgery. There were no cases of malignant transformation of an existing meningioma or radiation-induced secondary tumor development.

Factors predictive of tumor progression in univariate analysis are displayed in Table 5. Prior resection was not predictive of tumor control (Fig. 2). Regarding tumor control, Youden indices demonstrated that the optimal breakpoint for tumor volume occurred at 14 cm³ (Fig. 3). In the Cox multivariable analysis, the covariates associated with tumor progression included presentation with any CN deficit from III to VI (HR = 3.78, 95% CI 1.91–7.45; $p < 0.001$), history of prior radiation therapy (HR = 12.06, 95% CI 2.04–71.27; $p = 0.006$), and tumor volume greater than 14 cm³ (HR = 6.86, 95% CI 0.88–53.36; $p = 0.066$; Table 5; Figs. 4 and 5).

Further Treatments Following SRS

During follow-up, 2 patients underwent fractionated radiation therapy for out-of-field tumor progression (3%), and 5 patients underwent resection for tumor progression (7%). All tumors resected after radiosurgery were confirmed to be WHO Grade I meningiomas. Three patients had evidence of radiological progression of ventriculomegaly, but none of these patients required a CSF diversion procedure.

Overall Outcome After SRS

Unfavorable outcome, defined as tumor progression and/or new or worsening decline in neurological function, was observed in 12 patients (18.8%), compared with 52 patients (81.2%) who had a favorable outcome. Of those

FIG. 1. Graph of tumor-free progression after GKRS.

with an unfavorable outcome, 7 patients (10.9%) exhibited both tumor progression and neurological decline.

Univariate predictors of unfavorable overall outcome (i.e., tumor growth and/or neurological decline) are detailed in Table 6. Statistically significant factors in univariate analysis for an unfavorable outcome included petroclival/parasellar location, prior radiotherapy, prior surgery, any CN deficit from III to VI, diplopia on presentation, preexisting seizures, pre-GKRS edema, and decreasing maximal and peripheral dose (Table 6). Patients with a history of resection before radiosurgery were significantly more likely to have an unfavorable outcome in univariate analysis (OR = 2.37, 95% CI 1.08–5.21; $p = 0.032$), but prior resection was not an independent predictor of outcome. Youden indices did not provide a significant cutoff for the dichotomized continuous variable “tumor volume” that yielded the optimal discrimination of overall outcome.

In the multivariate analysis, the factors predictive of unfavorable outcome included history of prior radiation

TABLE 5. Predictors of tumor progression

Predictive Factor	HR	95% CI	p Value
Univariate analysis*			
Location			
All other locations	1.00		
Parasellar/pteroclival	5.11	0.65–39.91	0.120
History of radiotherapy	3.73	1.00–13.94	0.050
History of hydrocephalus	1.19	1.00–1.41	0.056
Any CN deficit from III to VI	3.29	1.79–6.05	<0.001
Diplopia on presentation	2.47	0.79–7.78	0.121
Seizure	7.64	1.53–38.04	0.013
Tumor volume >14 cm ³	6.86	0.88–53.36	0.066
Decreasing maximal dose	0.93	0.85–1.02	0.117
Multivariate analysis			
History of radiotherapy	12.06	2.04–71.27	0.006
Any CN deficit from III to VI	3.78	1.91–7.45	<0.001
Tumor volume >14 cm ³	6.86	0.88–53.36	0.066

* Factors predictive of tumor progression ($p < 0.20$).

FIG. 2. Graph of tumor-free progression in patients with and without a history of surgery.

therapy (OR = 3.39, 95% CI 1.11–10.39; $p = 0.033$), presentation with any CN deficit from III to VI (OR = 4.88, 95% CI 1.13–20.99; $p = 0.033$), and decreasing maximal radiosurgical dose (OR = 0.78, 95% CI 0.66–0.93; $p = 0.006$). Because maximal dose was not completely linear and overall outcome also depended on patient and tumor characteristics, Youden indices did not identify an optimal breakpoint for maximal dose that was applicable to all tumors.

Discussion

Traditionally, meningiomas are treated with upfront surgery with the goal of complete resection.^{7,9,40,41,53} Primary extirpation remains the gold standard of treatment for meningiomas. However, gross-total resection is often not possible. SRS has offered a viable alternative as well as an approach to achieve tumor control, especially for meningiomas that are challenging to resect such as those of the skull base.^{1,21,25,27,34,35,56} Combinations of microsurgery and SRS may yield even greater local control for select meningiomas arising from the cranial base.^{11,17,23,29,33,37,44} One such large study from the University of Pittsburgh with 972 patients, mostly with skull base meningiomas, reported actuarial tumor control rates of 93% at 5 years and 87% at 10 and 15 years.³³ However, the majority of meningioma SRS studies have not differentiated tumors by size, and many patient series exclude tumors of larger volume. Most radiosurgical series, in fact, include only small to moderately sized meningiomas under 8 cm³ in total volume (i.e., less than an average diameter of 2.5 cm).

Stratifying meningiomas by size is expected to yield different GKRS planning and prognostic outcomes, especially in confined areas such as the skull base. A recent study by Oya and colleagues reported that initial meningioma diameters greater than 25 mm was a factor associated with a short time to progression ($p = 0.0004$) and a higher annual growth rate ($p < 0.0001$).⁴² This finding confirms earlier multivariate analysis that linked lower rates of tumor control with higher tumor volume.²⁹ Other studies, including one from the University of Pittsburgh, have found that tumor volume greater than 8 cm³ was the most

FIG. 3. Graph of tumor-free progression in patients stratified by tumor volume of 14 cm³.

important parameter associated with a worse prognosis for radiosurgery of benign meningiomas.^{8,15,16,20}

From 1989 through 2012, our Gamma Knife center treated 75 patients with meningiomas at least 8 cm³ in volume at initial planning (mean preradiosurgical tumor volume = 14.1 cm³). Forty percent of patients were treated with primary radiosurgery, and the remaining 60% were treated following resection. This division of primary radiosurgery and combination therapy patient populations was consistent with previous reports.^{8,11,17,23,29,37,44} At last radiological follow-up (mean follow-up duration 6.5 years), 84% displayed no change or a decrease in tumor volume on MRI, and 16% demonstrated an increase in volume. Our extended period of follow-up more accurately accounts for the known long-term natural history and recurrence rates of these Grade I meningiomas. Radiological progression-free survival rates at 5 and 10 years were determined to be 89% and 77%, respectively. In the Cox multivariate analysis, the covariates associated with tumor progression included presentation with any CN deficit from III to VI, history of radiotherapy, and tumor volume greater than 14 cm³. These results in terms of tumor control for large meningiomas are promising, and at least for skull base meningiomas, the results appear to challenge traditional dogma relegating radiosurgery only to small or moderately sized tumors. When prior resection is undertaken, meningioma reduction to a volume of 14 cm³ or less appears to result in a reasonable target volume for single-session radiosurgery.

Our results appear to be comparable with other studies of radiosurgery for large meningiomas.^{8,16,20,45,52} Two small series with a mean follow-up of approximately 30 months reported 100% tumor control of all meningiomas with volumes greater than 10 cm³.^{45,52} Another study with longer follow-up by Haselsberger et al. similarly found excellent tumor control with staged GKRS for large benign meningiomas.²⁰ Of their 20 patients with treatment volumes between 5.4 and 43 cm³ (median 19 cm³), tumor control was achieved in 90% of cases. The 2 patients who initially experienced tumor progression in areas outside of the planning target volumes ultimately received additional radiosurgical procedures that resulted in subsequent tumor volume control. Ganz et al. reported 100% tumor

FIG. 4. Graph of tumor-free progression in patients with and without a history of radiotherapy.

FIG. 5. Graph of tumor-free progression in patients with and without a history of CN III, IV, V, or VI palsy on presentation.

control in their 97 patients with meningiomas greater than 10 cm³ and a mean follow-up of 4.5 years.¹⁶ Tumor regression was observed in 28% of tumors at last radiological follow-up. An institutional review of large-volume benign meningiomas at the Mayo Clinic reported tumor control rates of 99% at 3 years and 92% at 7 years after radiosurgery.⁸ The mean tumor margin dose was 15.1 Gy, and the mean preradiosurgical tumor volume was 17.5 cm³. These investigators found no factors to be associated with tumor growth after radiosurgery. Iwai et al. presented 7 cases of large petroclival or cavernous sinus meningiomas treated with staged GKRS.²⁴ Six patients (86%) did not have any tumor growth on last imaging. Unfortunately, the duration of their follow-up period (mean 39 months) limits the significance of these results, given the slow growth pattern of meningiomas and long-term mechanism of GKRS.

At last clinical follow-up, 83% of patients in this current series demonstrated improvement or no change in their neurological condition and 17% showed deterioration. Also, 4 patients had new or worsened peritumoral edema following radiosurgery. In multivariate analysis, history of surgery, presentation with any CN deficit from III to VI, and decreasing maximal dose were factors predictive of new or worsening decline in neurological condition. Tumor progression was present in 64% of patients who experienced new or worsening neurological decline. Unfavorable outcome (i.e., tumor progression or new or worsening decline in neurological function) was observed in 19% of patients. In the multivariate analysis, history of radiotherapy, presentation with any CN deficit from III to VI, and decreasing maximal dose were predictive of unfavorable outcome. Our clinical results are comparable to similar patient populations.^{8,16,20,45} Pendl et al. reported 88% clinical improvement or stability and 2 patients with new CN deficits (facial and optic nerve) at last clinical follow-up (mean of 28 months).⁴⁵ Haselsberger et al. reported that 45% of patients saw clinical improvement and 55% remained clinically stable at last follow-up (median of 7.5 years).²⁰ Commonly reported complications included transient nausea and emesis immediately posttreatment, peritumoral edema that often resolves within the first 6 months, headaches, and CN deficits. Three of the 97 patients in the study by

Ganz et al. suffered adverse radiation effect (i.e., post-SRS edema), all of which resolved completely within the follow-up period.¹⁶ Bledsoe et al. reported a complication rate of 23% after radiosurgery.⁸ Their complications, in order of decreasing frequency, included seizures, hemiparesis, trigeminal injury, headaches, diplopia, cerebral infarction, ataxia, and hearing loss. When analyzing their series by tumor location, they noted a statistically significant difference in complication rates between patients with supratentorial tumors and those with skull base tumors (44% vs 18%, respectively). This data further supports reasonably safe management of large-volume skull base meningiomas with radiosurgery.

Radiological and clinical outcomes from our and other

TABLE 6. Predictors of overall outcome

Predictor of Unfavorable Outcome*	OR	95% CI	p Value
Univariate analysis†			
Location			
All other locations	1.00		
Parasellar/petroclival	8.07	0.97–67.18	0.054
History of radiotherapy	5.44	0.95–31.36	0.058
History of surgery	2.37	1.08–5.21	0.032
Any CN deficit from III to VI	3.52	1.58–7.80	0.002
Diplopia on presentation	2.71	0.75–9.82	0.128
Seizure	10.20	0.84–123.56	0.068
Pre-GKRS edema	2.99	0.69–12.89	0.142
Decreasing peripheral dose	0.68	0.61–1.02	0.068
Decreasing maximal dose	0.85	0.74–0.97	0.019
Multivariate analysis			
History of radiotherapy	3.39	1.11–10.39	0.033
Any CN deficit from III to VI	4.88	1.13–20.99	0.033
Decreasing maximal dose	0.78	0.66–0.93	0.006

* Favorable outcome = tumor control and no new or worsening decline in neurological function.

† Factors predictive of unfavorable outcome ($p < 0.20$).

presented series of large meningiomas are similar to those obtained in series of smaller meningiomas of the skull base.^{11,17,23,29,33,37,44} We surmise that these results are similar due to advances in radiosurgical technology that have focused on more accurate targeting and limiting unnecessary radiation to nearby viable tissue. The goal of GKRS for large-sized meningiomas is similar to that of smaller lesions, which is to prevent tumor progression without incurring radiosurgical morbidity by reducing the margin dose. However, radiosurgical planning of larger tumors requires particular attention to tumor location and surrounding structures. Optimal planning requires consideration of achieving optimal dose gradients and varying them when prudent. For example, for a large skull base meningioma, the dose gradient in the direction of the brainstem with critical neurological structures may need to be steeper than that to the petrous bone, with fewer at-risk structures.

Typically, large meningiomas cause local mass effect to which the brain adapts and may even continue to function normally as growth gradually occurs over many years. This means surrounding structures may still be viable but are closely approximated to the tumor, thereby increasing the difficulty of complete resection. Over the last few decades, improved precision of radiosurgical planning has helped to minimize radiation overlap. Highly conformal dose planning has permitted effective coverage of irregularly shaped tumors and even dural tails to be included within the prescription isodose line. DiBiase et al. noted that inclusion of the dural tail in the treatment volume rendered a significantly higher 5-year disease-free survival score than not including the tail (96% vs 78%, respectively).¹³ Furthermore, the trend of reduced marginal doses to around 12 Gy has proven just as efficacious for tumor control as higher doses, while limiting radiation dosage to nearby neurovascular structures.^{22,28,46} Ganz et al. recommended that the marginal dose be kept at 12 Gy and only reduced if it was necessary to protect normal tissue.¹⁶

Hypofractionated or multisession radiosurgical procedures also offers steep radiation falloff to protect adjacent tissue from radiation-induced injury.^{24,43,45} Multisession radiosurgery may allow for effective management of larger skull base meningiomas. Even when benign meningiomas are discovered at larger sizes, their lack of invasion and clear visualization on neuroimaging permit complete radiation coverage of the tumor cells.

Our study is one of the largest radiosurgical series of large skull base meningiomas to date. However, this study remains limited by its retrospective nature and by institutional selection and treatment biases. Additionally, in this study we sought to determine the outcomes following planned single-session radiosurgery, and thus we did not include patients with multisession treatment plans or fractionated radiosurgery. The treatment period of this study also includes over two decades of treatment, and during this period, GKRS technology, radiosurgical technique, and neuroimaging have generally improved. Only a small set of select patients were only evaluated by pre- and post-treatment CT scans. Contouring of the tumor volume is also a potential source of bias. We are unable to reliably determine how refinements in GKRS units, treatment planning, neuroimaging, and targeting strategies may have

altered our outcomes. Additionally, a number of posttreatment effects of frame-based radiosurgery such as headache, pin site infection, and fatigue were not routinely captured as part of this study; unfortunately, we do not have sufficient data to fully account for these types of complications. Additional neuropsychiatric and electrophysiological testing would be beneficial to further define potential subtle complications. Finally, it is not clear whether these results for large skull base meningiomas are generalizable to large meningiomas involving other intracranial locations. In particular, large parasagittal and parafalcine meningiomas that are in close proximity to large venous structures have been previously shown to have greater risk of symptomatic postradiosurgical peritumoral edema.¹⁴ Further assessment of large patient cohorts may be necessary to fully define the edema risk in skull base lesions in close proximity to key deep and large venous structures

Conclusions

Stereotactic radiosurgery affords a reasonable rate of tumor control for large skull base meningiomas, and it accomplishes this with an acceptably low incidence of neurological deterioration. Surgery may be the preferred treatment option for lesions larger than 8 cm³ (an approximate tumor diameter of 2.5 cm) when patients have growing and symptomatic lesions (e.g., those presenting with any CN deficit from III to VI). However, in cases of enlarging asymptomatic lesions, recurrent or residual lesions following resection, significant patient comorbidities, and patient preference, SRS demonstrates reasonable results for large meningiomas.

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