


# Linear Accelerator-Based Stereotactic Radiotherapy for Low-Grade Meningiomas: Improved Local Control With Hypofractionation

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## ABSTRACT

**BACKGROUND AND PURPOSE:** Meningioma is a common type of benign tumor that can be managed in several ways, ranging from close observation, surgical resection, and various types of radiation. We present here results from a 10-year experience treating meningiomas with a hypofractionated approach.

**MATERIALS AND METHODS:** We reviewed the charts of 56 patients treated with stereotactic radiosurgery (SRS) or hypofractionated stereotactic radiotherapy (SRT) from 2008 to 2017. A total of 46 (82%) patients had WHO Grade 1 disease and 10 (18%) had Grade 2. Outcomes that were analyzed included local control rates and the rate and grade of any reported toxicity.

**RESULTS:** A total of 38 women and 18 men underwent SRS to a median dose of 15 Gy ( $n = 24$ ) or hypofractionated SRT with a median dose of 25 Gy in five fractions ( $n = 34$ ). Of the 56 patients, 22 had surgery before receiving treatment. The median follow-up was 36 (6–110) months. Local control at 2 and 5 years for all patients was 90% and 88%, respectively. Comparing fractionated to single-fraction treatment, there was improved local control with fractionation (91% vs 80% local control at 2 years,  $P = .009$ ). There was one episode of late radionecrosis on imaging with associated symptoms after single-fraction treatment and one patient requiring resection of meningioma related to worsening symptoms (and local recurrence) after five-fraction SRT.

**CONCLUSIONS:** This study provides further evidence for high rates of local control and minimal toxicity using a hypofractionated SRT approach, with improvement in local control through use of hypofractionation.

**KEYWORDS:** Meningioma, stereotactic radiosurgery, hypofractionated

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## Background and Purpose

Meningiomas are the most common primary central nervous system tumor, accounting for about 26,000 new cases per year in the United States.<sup>1</sup> They are typically benign, with the vast majority (80%–90%) being World Health Organization (WHO) Grade 1.<sup>2</sup> Despite being benign, their location in the central nervous system can lead to serious complications, and treatment is often warranted. When approaching patients diagnosed with meningioma, care must be taken to find the appropriate balance between definitive treatment and avoidance of therapeutic-related neurologic damage. As a result, patients with small, asymptomatic meningiomas are preferably observed, reserving treatment for clinical or radiographic progression.<sup>3</sup>

For patients requiring up-front treatment, the management strategy may consist of surgery, surgery plus radiation therapy, or radiation therapy alone. In terms of radiotherapy, stereotactic radiosurgery (SRS) offers a treatment solution that delivers a conformal high dose of radiation in a single fraction with

rapid falloff, thus sparing the adjacent normal brain parenchyma or nearby critical structures.<sup>4</sup> As such, SRS has a well-established role in the management of meningiomas.<sup>5–7</sup> Alternatively, conventional fractionated radiotherapy is typically employed when there is concern for normal tissue injury, as a consequence of large tumor size or anatomic proximity to organs at risk.<sup>8–10</sup> More recently, hypofractionated stereotactic radiotherapy (SRT) has emerged as another possible treatment solution.

Essentially a fractionated derivative of SRS, SRT allows for delivery of conformal, high dose per fraction radiation treatments, typically in two to five fractions. Available data on this approach are limited compared to SRS; however, results appear to be promising in terms of safety and efficacy.<sup>11–13</sup> Over the last decade, patients diagnosed with meningioma and treated with radiotherapy have typically been managed with this hypofractionated approach at our institution. Herein, we present the results of our experience using SRT in the management of meningioma.



## Methods

### Patient population

From 2008 to 2017, a total of 56 patients aged 38 to 87 (median age of 62) years were treated with linear accelerator-based SRS (39%) and hypofractionated SRT (61%) for meningioma in this institutional review board (IRB) approved retrospective study (IRB number: 2018-177). The median Eastern Cooperative Oncology Group (ECOG) performance status grade was 1 (range: 0-3). Prior surgical resection was performed in 22 patients (39%), with a median time between completion of surgery and initiation of radiation of 36 (1-288) months. Lesions were located in the cerebral hemispheres (n=25), parasagittally (n=19), or at the skull base (n=12).

### Treatment planning

Our methods for brain SRS/SRT have been previously described, and are as follows.<sup>14</sup> Before treatment, a contrast-enhanced (i.e. gadolinium) T1-weighted neuronavigation magnetic resonance imaging (MRI) was performed with a resolution of 0.5 mm by 0.5 mm and a slice thickness of 1 mm. Once the MRI was acquired, a planning computed tomography (CT) simulation was performed. During planning CT simulation, patients were immobilized using a Brainlab (Feldkirchen, Germany) relocatable mask system. Subsequently, a mouth bite apparatus was placed against the upper dentition to prevent head tilt movement. Use of the mouth bite was omitted if the patient was unable to tolerate its presence. In addition, a customized thermoplastic mask was molded to conform to the contours of the patient's head. Once the patient was immobilized, CT images were acquired utilizing a resolution of 1 mm by 1 mm and a slice thickness of 2 mm. After CT image acquisition, the images were co-registered to the MRI data set in the Brainlab iPlan image software.<sup>14</sup> The treating radiation oncologist then contoured the gross target volume (GTV), which was expanded by a margin of 2 mm to generate the planning target volume (PTV). A treatment plan using 4 to 10 non-coplanar conformal arcs was generated using pencil beam algorithm in Brainlab iPlan Dose software.<sup>14</sup> Once the treatment plan was complete, patients were treated to a median dose of 25 Gy (range: 13-27.5 Gy) in five fractions (range: 1-5), prescribed to the 80% to 100% isodose line (median PTV of 7.245 [range: 0.8-55.0] cc). To ensure appropriate target alignment, megavoltage cone beam imaging was used before the delivery of treatment. Follow-up included surveillance MRIs and clinical assessments every 3 to 6 months for the first 2 to 3 years and then yearly thereafter.

### Statistical analysis

Each patient's record was reviewed to assess local control and overall survival from time of SRS/SRT. Local failure was defined as radiographic enlargement of  $\geq 2$  mm on follow-up

**Table 1.** Patient characteristics.

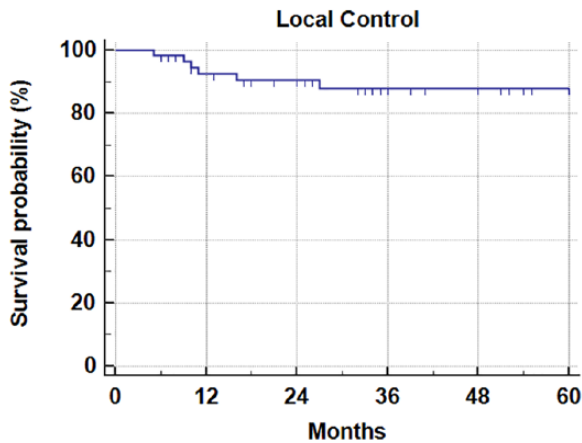
PATIENT CHARACTERISTICS	VALUES (%)
Sex	
Male	18 (32)
Female	38 (68)
ECOG	1 (0-3)
Size (cm)	2.2 (0.5-6.0)
Age (years)	62 (38-87)
Location	
Cerebrum	25 (45)
Parasagittal	19 (34)
Skull Base	12 (21)
Prior resection	
Yes	22 (39)
No	34 (61)
Time from surgery to SRS (months)	36 (1-288)
WHO Grade	
1	46 (82)
2	10 (18)
Target volume (cc)	7.245 (0.8-55)
Fractionation and dose	
Single fraction	24 (39) to median 15 (13.5-16) Gy
Three to five fractions	32 (61) to median 25 (21-30) Gy

Abbreviations: ECOG, Eastern Cooperative Oncology Group; WHO, World Health Organization.

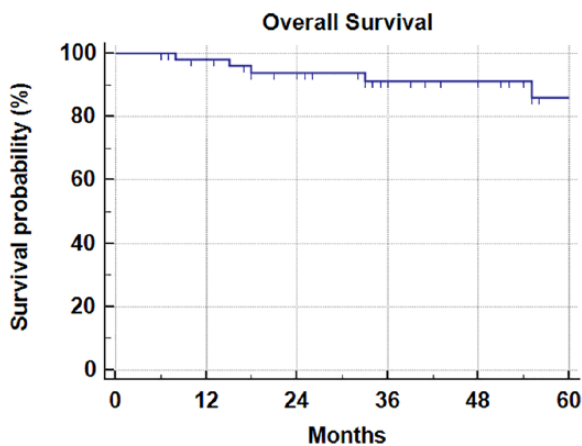
imaging after review by both radiation oncology and neuro-radiology. Statistical analysis was completed using Medcalc statistical software V18 (Ostend, Belgium). Multivariate Cox<sup>15</sup> and Kaplan-Meier<sup>16</sup> regressions were used to determine overall survival (OS) and local control, as well as any possible predictors including size, volume, dose, age, sex, and number of fractions. Toxicity data were also recorded from clinical follow-up notes and documented according to the common terminology criteria for adverse events (CTCAE), version 5.0.

## Results

A total of 56 patients were treated with either SRS of hypofractionated SRT over a 10-year period at our institution. Patient and treatment characteristics are outlined in Table 1. The majority of patients (61%) were treated with a hypofractionated approach, with a median dose of 25 Gy in five fractions (range: 13-27.5 Gy in one to five fractions). A total of nine patients (16%) had confirmed Grade 2 meningioma. A



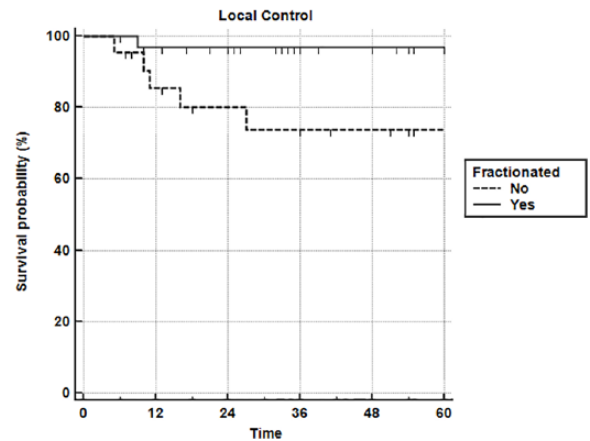
**Figure 1.** Local control after SRS/SRT for meningioma. Local control was 90% and 88% at 2 and 5 years, respectively.



**Figure 2.** Overall survival from time of radiation. Five-year overall survival was 86% across the entire group.

total of 14 patients had pathologically proven Grade 1 disease, with the remainder having presumed Grade 1 meningioma. By treatment schema (single fraction versus multi-fraction) median dose was 14.5 (13-16) Gy and 25 (21-30) Gy, respectively. In terms of tumor size, median volume was 6.05 (0.8-13.5) cm<sup>3</sup> and 7.35 (1.93-55) cm<sup>3</sup> for the single-fraction and multi-fraction cohorts, respectively.

The median follow-up after completion of radiation treatment was 36 (6-110) months. Every patient had follow-up imaging available for review, with median number of available studies being 4 (1-16). Five patients with Grade 1 disease and one patient with Grade 2 disease had local failure. Local control for all patients was 90% at 24 months and 88% at 60 months (Figure 1). At the time of analysis, five patients (10%) were confirmed dead either by medical records or posted obituaries. Actuarial survival at 2 and 5 years from radiation was 94% and 86%, respectively (Figure 2). Cause of death was unknown in four cases and unrelated to meningioma in the additional confirmed case (metastatic lung cancer). Treatment was well tolerated with no  $\geq$ Grade 3 acute toxicity, and two episodes of late Grade 3 toxicity in the form of



**Figure 3.** Local control based on single-fraction versus hypofractionated radiation. At 2 years local control was 90% compared to 80% ( $P=.0196$ ).

radionecrosis, one of which required surgical intervention 10 months after five-fraction radiation to 27.5 Gy. The other patient developed surrounding edema and resultant seizure activity 4 months after single-fraction SRS to 14 Gy. On univariate analysis, fractionated treatment had improved local control across the cohort, with local control of 91% compared to 80% at 2 years,  $P=0.0196$  (Figure 3). Multivariate analysis confirmed fractionation as a predictor for improved local control, hazard ratio (HR)=0.031, 95% confidence interval (CI),  $P=.009$ , as well as prior surgery ( $P=.034$ ). On multivariate analysis (Table 2), predictors of local failure were lesions  $>2$  cm and patients who did not undergo prior resection ( $P<.05$ ). Target volume size, age at time of SRS, and sex were not predictive of worse local control. Likewise, no predictors of increased toxicity were identified.

## Discussion

Meningiomas are the most common primary central nervous system tumor, with the vast majority being benign WHO Grade 1.<sup>1,3</sup> Often, meningioma is an incidental finding on imaging which was obtained for another purpose.<sup>17</sup> Typically, if the lesion is small and in a favorable anatomic location, observation is the preferred management strategy.<sup>17,18</sup> To that end, a series from Germany followed nearly 50 patients with incidentally discovered meningiomas and reported an annual growth rate of about 1 cm<sup>3</sup> per year.<sup>17</sup> Of note, initial tumor size was not found to be a predictor of growth rate, thus supporting observation as a reasonable approach.<sup>17</sup>

Despite the indolent nature of most meningiomas, problems may arise if they are large or near critical structures such as the brainstem or optic pathway. In instances where symptoms are present, or likely to occur with any growth, surgery is the preferred option when feasible. A large series from Finland examined outcomes in more than 900 patients who underwent surgery for intracranial meningiomas showing excellent long-term local control of 90% with operative mortality of 7%.<sup>19</sup> A similar surgical series from the Mayo Clinic with 581 patients

**Table 2.** Multivariable Cox regression analysis for local control.

PARAMETER	HAZARD RATIO (95% CI)	P VALUE
Location		
Parasagittal	Reference	–
Cerebrum	0.73 (0.10–5.42)	.76
Skull base	1.94 (0.09–44.5)	.68
Prior resection		
No	Reference	–
Yes	0.06 (0.005–0.81)	<b>.03</b>
Grade		
I	Reference	–
II (atypical)	11.72 (0.48–284)	.13
Fractionation		
Single (SRS)	Reference	–
3–5 (SRT)	0.03 (0.002–0.42)	<b>.01</b>
Size		
≤2 cm	Reference	–
>2 cm	30.22 (1.64–556)	<b>.02</b>

Abbreviations: CI, confidence interval; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy.

Note: All bold values are below 0.05, therefore they are considered statistically significant.

showed progression-free survival of 75% at 10 years, with perioperative mortality (<2%).<sup>20</sup> Following surgical resection, careful attention must be paid to the Simpson resection grade, as recurrence rates can be as high as 30% to 35% for grade III and IV (complete resection without coagulation of dural attachment and subtotal resection, respectively).<sup>21</sup> In those situations, careful follow-up is needed, with consideration of adjuvant treatment in the form of radiation.<sup>22</sup>

Radiation can be used in the definitive management of meningioma as well, with a more conventional approach of approximately 50 Gy in 25 to 28 daily fractions. Outcomes in a group of over 300 patients treated to a median dose of 57.6 Gy showed local control rates of 93% at median follow-up of 5.7 years.<sup>10</sup> Approximately 40% of patients with pre-existing neurologic deficits showed improvement following treatment, with <10% of patients experiencing exacerbation of symptoms.<sup>10</sup> Similarly, a series investigating radiotherapy in cases of “imaging-defined” meningiomas reported 8-year local control rates of 94% with no significant treatment-related toxicity in tumors treated to a dose of 50.4 Gy.<sup>8</sup>

Of note, both the previously mentioned series included patients dating back to 1985, before the advances in both imaging and radiation technology. With those advances came the

technique of SRS, first in the form of the gamma knife (GK), soon to be followed by the Cyberknife and linear accelerator-based systems.

The GK has long played a role in the definitive management of meningiomas. A series from the University of Pittsburgh reported on outcomes in more than 900 patients with more than 1000 meningiomas treated for almost 20 years.<sup>5</sup> As expected, the vast majority of cases were Grade 1, and local control at 18 years was 93%. Treatment was well tolerated, and treatment-related symptoms developed in only 4% of cases. A similar series from the Mayo Clinic was published looking at outcomes in 600 patients treated over 18 years, with ~80% representing proven or presumed Grade 1 meningiomas.<sup>7</sup> The median dose delivered was 16 Gy. Results were again excellent, with 94% local control. Treatment was well tolerated with 11% experiencing radiation-related complications. Of note, predictors for toxicity included larger tumor size and lesions in the parasagittal/falx region. The same group of authors also published outcomes using single-fraction GK SRS for larger volume (defined as >10 cm<sup>3</sup>) meningiomas.<sup>23</sup> The series included more than 100 patients, and the median dose was 15 Gy. At 7 years, local control was 92%, but of note, 23% of patients had serious complications including hemiparesis, cranial nerve injury, cerebral infarction, and hearing loss. The authors commented on the relative safety of the technique, but recommended surgery as primary treatment for such large lesions.

With advances in radiation therapy, a hypofractionated approach (defined arbitrarily in the United States as 2–5 treatments) has been slowly implemented into the treatment of intracranial lesions across essentially all treatment platforms. At least theoretically, the use of multiple fractions should potentially be safer, especially in large tumors or those in a precarious location. An Italian study published just this year examined outcomes in 52 patients treated using the Cyberknife system.<sup>24</sup> They delivered single-fraction SRS for lesions <2 cm and fractionated treatment for those lesions >2 cm. With a follow-up of 20 months, local control was estimated to be 90% at 3 years and baseline tumor-related symptoms improved in up to 50%. Given, the small number of failures, no differences were noted between single-fraction or hypofractionated schedules. Another study from Pittsburgh also presented Cyberknife outcomes for 73 meningioma patients (82% Grade 1) treated to a median dose of 24 Gy in three fractions.<sup>11</sup> Local control for Grade 1 lesions was 95% at 1 year with a single episode of late Grade 3 toxicity. Similarly, groups from Germany and Italy reported on a large series of patients treated in a hypofractionated manner with expected high rates of local control (>90%) and low toxicity (<5%).<sup>25,26</sup>

We would be remiss not to mention some fundamental differences between the GK and linear accelerator-based SRS/SRT, namely, that linear accelerator-based radiosurgery has a more homogeneous isodose and prescription coverage, while the



GK technique uses similar/identical marginal doses but with a significantly higher maximum point dose given prescription to the 50% isodose line. More recently, the GK which has traditionally been a single-fraction device (outside of staged treatments which are 1 month apart), has been increasingly used in a hypofractionated manner.<sup>12,13</sup> A group from South Korea reported on outcomes in 70 patients with tumors >10 cm<sup>3</sup>.<sup>12</sup> Of those patients, 60% were treated in a single fraction to 12 Gy, and the remaining patients were treated in two to four fractions, total doses ranging from 15 to 18 Gy. The fractionated group had a numerically higher rate of local control at 5 years (93% vs 88%,  $P=.389$ ). A lower complication rate was noted with fractionation, 7% compared to 33%,  $P=.017$ . Another GK user group from Seoul, South Korea also published outcomes on a small group of 23 patients with meningiomas >10 cm<sup>3</sup>, all treated in a hypofractionated fashion.<sup>13</sup> The median dose was 18 Gy in three fractions and follow-up was 38 months. No patients experienced local failure in follow-up. Treatment was very well tolerated, with only 17% of patients experiencing transient cranial neuropathy (trigeminal being most common).

The results of our study mirror those discussed above, and represent one of the larger series' examining outcomes using a primarily hypofractionated approach. The local control was excellent, as expected, and even seemed to be improved with a fractionated approach. Similarly, serious toxicity was quite low at <5% (2 of 59 patients) lending further support for a hypofractionated approach in the appropriate patient. However, one must keep in mind that not all of the targets in the present series were large (>10 cm<sup>3</sup>) as in some of the previously described studies. Median volume in our cohort was 7.2 cm<sup>3</sup>, but some large lesions were included with largest being 55 cm<sup>3</sup>. We must also acknowledge that almost all long-term safety and efficacy data come from single-fraction treatment which provides more than ample evidence for such an approach. In addition, this is a retrospective series which inherently includes a selection bias. Furthermore, median follow-up was 36 months, which is relatively short for a generally indolent tumor such as meningioma. As such, we advise further follow-up to continue documentation of durable local control and low toxicity.

## Conclusions

Hypofractionated SRT remains a safe and effective treatment option for patients with meningioma. Its use is preferred over SRS in cases of larger (>10 cm<sup>3</sup>) tumors or when tumors abut critical structures. Hypofractionation, at least in the present series, was associated with improved local control when compared to SRS.

## Author Contributions

REW was responsible for project conception and design, data analysis and interpretation, and drafting the manuscript. SAb, RF, and RWW contributed to drafting the manuscript. SAn and SH contributed to the data analysis and drafting the

manuscript. SMK contributed to drafting the manuscript and gave the final approval for the manuscript.

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