



## Linear Accelerator–Based Radiosurgery of Grade I Intracranial Meningiomas

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■ **OBJECTIVE:** To determine the local control rate and complication rate in the treatment of grade I intracranial meningiomas.

■ **METHODS:** A retrospective study was performed of patients with grade I meningioma who received radiosurgery with a dedicated linear accelerator from January 2002 to August 2012 with a minimum follow-up of 2 years. We performed descriptive statistics, logistic regression, and progression-free survival analysis through a Kaplan-Meier curve.

■ **RESULTS:** Seventy-five patients with 78 grade I meningiomas received radiosurgery, 39 underwent surgery plus adjuvant radiosurgery, and 36 only radiosurgery. The follow-up median time was 68 months (range, 35–120 months). The tumor control rate was 93%, the 5-year progression-free survival was 92% (95% confidence interval, 77%–98%). Acute toxicity was 2.6%, and grade 1–2 late toxicity was 26.6%. Postradiosurgery edema was the main late morbidity. Age >55 years was the only significant factor for attaining a response >75%. The background of surgery before radiosurgery was the only significant prognostic factor for showing edema (odds ratio 5.78 [95% confidence interval, 2.14–15.64]).

■ **CONCLUSIONS:** The local control rate attained in our series is similar to that reported in other series worldwide; the acute toxicity rate was low and late toxicity was moderate.

### INTRODUCTION

Meningiomas represent from 13% to 26% of all intracranial neoplasias. Intracranial meningiomas are the most common benign tumors in adults. They are more common in women than in men and their appearance generally occurs between the fourth and sixth decades of life; their incidence increases with aging.<sup>1</sup> Microsurgery is the first treatment option for many meningiomas, although the decision depends also on their size and location. The key to success in the treatment of intracranial meningiomas lies in the degree of resection. The ideal procedure is a macroscopically complete resection, including the dura mater with its implant without a postoperative neurologic deficit.<sup>2</sup> The histologic degree and the extent of the resection seem to be the main prognostic factors for forecasting recurrence.<sup>3</sup> When complete resection is not possible, treatment with radiosurgery (RS) or a combined surgery and RS treatment for the residual tumor must be considered. Multidisciplinary assessment has major possibilities of obtaining satisfactory results because both surgery and RS have to be considered as complementary treatments for patients with intracranial meningiomas.<sup>4</sup> When there are neurologic symptoms by compression of meningioma, surgery is the best option.<sup>5</sup> Another treatment alternative is radiotherapy when the tumor is large and cannot be operated on or when meningiomas have a confirmed World Health Organization (WHO) grade II or III.<sup>6</sup> RS may be used in tumors with small volume and difficult surgical access or that are incompletely resected or recurrent.<sup>7,8</sup> In Mexico, there are only reports on the response to meningioma treatment based on the surgical experience of different research groups and only 1 study with RS in which 22 meningiomas were analyzed together with other neoplasias.<sup>9–12</sup>

### Key words

- Benign tumors
- LINAC radiosurgery
- Meningiomas

### Abbreviations and Acronyms

- CBK:** CyberKnife
- GKRS:** Gamma Knife radiosurgery
- LINAC:** Linear accelerator
- MRI:** Magnetic resonance imaging
- PFS:** Progression-free survival
- RS:** Radiosurgery
- WHO:** World Health Organization

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This study shows the experience at Instituto Nacional de Neurología y Neurocirugía, Mexico City, 16 years after the adoption of RS in the treatment of meningiomas using a dedicated linear accelerator (LINAC) to value the local control rate and follow-up complications.

## METHODS

On approval by the ethics committee of Instituto Nacional de Neurología y Neurocirugía, an observational retrospective longitudinal study, which included all patients older than 18 years with a diagnosis of intracranial meningioma treated with RS at the radioneurosurgery unit of our hospital was made between January 2002 and August 2012 with at least 2 years of follow-up.

The diagnosis was established by means of a histopathologic study or through magnetic resonance imaging (MRI) in patients without previous surgery. The prescribed dose was administered to each patient in a single fraction by means of a 6-MV Novalis (Brainlab, Munich, Germany) linear accelerator with the stationary framework iPlanDose 4.1 (Brainlab) planning system.

Studied variables were age, gender, location of the meningioma,<sup>13</sup> previous surgery, Simpson classification, histologic subtype, initial volume before the RS, volume at 6, 12, 18, 24, and 36 months after RS, volume at the moment of the last assessment, complications after RS, recurrence, edema volume after radiosurgery, and change between initial and final volumes.

Both clinical and radiologic follow-up of patients were performed in regular time intervals. All patients were seen 1 month later after the RS to assess the presence of acute toxicity secondary to the procedure and an MRI was performed as part of their follow-up at 6, 12, 18, 24, and 36 months, then every year until 5 years, and then every 2 years until the last assessment. The primary result of the study was local control of the tumor measured from the date of treatment until the date of local recurrence or last MRI, both measured by volumetry with iPlanImage 4.1.

We define as stable the widely accepted criterion of reduction or increase of  $\pm 10\%$  compared with the initial volume. We define a minor response as a volume decrease between 11% and 74% compared with the initial volume, major response as a decrease of 75%–89%, and progression as an increase in lesions of  $>11\%$  of the initial volume.

## Statistical Analysis

A descriptive statistical analysis of the demographic characteristics of the study group was performed. The averages of initial and final volumes were compared on MRI through a paired Student *t* test.

The tumor reduction percentage was estimated at the end of the follow-up compared with the initial volume with a  $\chi^2$  test.

Also, both a bivariate and multivariate logistic regression were performed to identify the factors that determine local control, progression, and presence of edema after RS by considering a significant  $\alpha$  value of 0.05 with 2 queues.

A bivariate logistic regression was performed to seek response, progression, and edema predictors by assessing variables associated with the patient (sex, age, comorbidity, and clinical symptoms); associated with the meningioma (topographic location, size, surgical handling background, histologic subtype, and Simpson degree when applicable); associated with the treatment

(RS volume, marginal doses, isocenter doses, maximum and minimum doses, homogeneity, conformality, number of fields, and technique).

A progression-free survival (PFS) analysis was performed through a Kaplan-Meier curve. The entire statistical analysis was performed with SPSS version 20 (IBM Corp., Armonk, New York, USA) by a researcher blinded to the results of the treatment (A.R.C.).

## RESULTS

A total of 288 patients with diagnosed meningioma were treated at the radioneurosurgery unit of Instituto Nacional de Neurología y Neurocirugía from 2002 to 2012. Their treatment comprised either RS alone or fractionated stereotactic radiotherapy. This study analyzed 108 patients who received RS. Of these 108 patients, the following were excluded: 5 who had  $>2$  meningiomas or meningioma associated with neurofibromatosis, 2 associated with cancer, 1 with atypical meningioma, 3 patients who had incomplete data, and 22 patients who did not have 24 months of follow-up by the time of the analysis. This study reports results of 75 patients and 78 meningiomas with a follow-up median of 68 months (range, 35–120 months). The clinical characteristics of patients are shown in Table 1.

The average age of all 75 patients was  $50.2 \pm 13.4$  years (range, 21–78 years). Eleven patients were male (15%) and 64 were women (85%). Of these patients, 39 had been previously treated with surgery and 36 had been treated with RS alone. The location of the meningiomas is shown in Table 1. Tentorial location, falx cerebri, and parasagittal locations prevailed, amounting to 53% of all locations. Of 75 patients, 61% had meningioma on the convexity and 39% on the base. The diagnosis was based on imaging in 36 patients, and 39 patients with previous surgery had a histopathology report. The initial symptoms in patients were cranial nerve deficits in 31 patients, headache in 30, seizures in 20, gait disturbances in 10, and paresis in 5.

The indication of RS in patients with previous surgical management was by recurrence in 11 (28%), symptom persistence after primary microsurgery in 25 (64%), and tumor progression in 3 (8%). Symptoms in all 25 patients with persistence after microsurgery were deficit of some cranial pair (36%), seizures (24%), headache (20%), mental disturbances (12%), and paresis (8%).

The decision to perform RS in patients with surgical background was performed in joint sessions of neurosurgery, RS, neuro-ophthalmology, neuro-otolaryngology, and neuroimaging services referred to as Tumor Board under the following considerations: in 18 of 42 meningiomas (43%), surgery was performed with a Simpson grade  $>3$ , and in 24 (57%), a total gross resection (Simpson grade 1–3) was performed. Patients who received surgery with Simpson grade 1 did not require RS; for patients with Simpson grade 2 or 3, if their location was considered as difficult to manage, especially when there were already recurrences, the choice was to give them complementary management with RS to try to avoid recurrences. In patients with Simpson grade 4 who were operated on, once their symptoms improved by decompression and if tumor extraction was not successful, RS was performed to prevent a recurrence of symptoms. As for patients with Simpson 5, after performing a biopsy was performed and the

**Table 1.** Clinical Characteristics of 75 Patients with 78 grade I Meningiomas

Variable	Only Radiosurgery (N = 36)	Microsurgery + Radiosurgery (N = 39)	Total (N = 75)
Gender, n (male/female)	1/35	10/29	11/64
Age (years)	53.2 ± 13.4 (23–78)	47 ± 12.8 (21–75)	50.2 ± 13.4 (21–78)
Localization, N (%)			
Tentorial	9	7	16 (20)
Falx cerebri	7	9	16 (20)
Parasagittal	4	5	9 (12)
Minor wing sphenoid	0	8	8 (11)
Cavernous sinus	6	1	7 (9)
Petroclival	3	3	6 (8)
Convexity	3	3	6 (8)
Cerebellopontine angle	3	1	4 (5)
Olfactory groove	0	2	2 (3)
Magnus foramen	0	1	1 (1)
Sellar tubercle	0	1	1 (1)
Sphenoid plane	1	0	1 (1)
Orbital	0	1	1 (1)
Radiosurgery indication			
Recurrence		11	
Persistence of signs and symptoms		24	
Progression		3	
Incidental		1	

histology identified, RS was administered as an alternative management because there were different reasons for surgical contraindications. All patients who initially showed peritumoral edema at the time of their diagnosis were treated with microsurgery.

When the location of meningiomas is considered for patients who were initially taken to surgery, comparing those located on the base with those on the convexity, only 4 of 15 (26%) of those located on the base had a total gross resection compared with 20 of 27 that were located on the convexity (74%,  $P = 0.002$ ) (i.e., residue was left in meningiomas located on the base in a statistically significant percentage compared with those located on the convexity).

Transitional, fibroblastic, and meningothelial histologic subtypes were reported in 18, 10, and 5 patients, respectively, comprising 85% of all patients with previous surgery. In 1 patient, the histologic result was an angiomatose meningioma, and the histology report is unknown in 5 patients (12%) because the surgery was performed in another hospital and they were sent only with diagnosis of WHO grade I meningioma without some specification of histologic subtype.

The average target volume was 4.49 cm<sup>3</sup> (range, 0.33–13.9 cm<sup>3</sup>) and the marginal dose median 16.2 Gy (range, 12–20.8 Gy). The

maximum dose median was 19.62 Gy (range, 15.5–26.6 Gy) and the average isocenter dose was 19 Gy (range, 13–26 Gy), with homogeneity (maximum dose/prescription dose) of 1.22 in average (range, 1.03–1.5). The concurrence index was 1.69 (range, 1.11–2.63). The techniques used were 50% of patients with conformal dynamic arc, 33% with conformal static fields, 9% with cones, and 8% with intensity-modulated radiation therapy. On choosing the curve that covers  $\geq 96\%$  of the dose as a service criterion, the maximum tolerance dose for risk organs (optical nerve <8 Gy, chiasm <8 Gy, cochlea <8 Gy, brainstem <12 Gy, and brain parenchyma <12 Gy) was not exceeded.

**Table 2.** Local Control Tumor in 78 Meningiomas

Initial Volume Reduction Rate (%)	Number	%	Classification
11–74	42	53	Minor response
75–89	23	30	Major response
±10	8	10	Stable response
Increment of >11 of initial volume	5	7	Progression

**Table 3.** Evolution of Mean Volume in 78 Grade I Meningiomas

Parameter	Mean ± Standard Deviation (cm <sup>3</sup> )	Range (cm <sup>3</sup> )
Target volume at radiosurgery	4.52 ± 3.3	0.33–13.9
6 months	4.40 ± 4.0	0.28–19.52
12 months	3.52 ± 3.3	0.27–14.27
18 months	3.20 ± 3.6	0.21–17.32
24 months	2.90 ± 3.5	0–17
30 months	2.50 ± 2.8	0–13.79
36 months	2.75 ± 3.8	0.27–16.32
Late revision	2.30 ± 2.5	0–11.8

### Tumor Control

The response defined by MRI as tumor volume reduction after RS and up to the last follow-up is shown in Table 2. Of 78 treated meningiomas, 73 (93%) had local tumor control. The MRI performed at the last follow-up or by the time of progression showed 8 meningiomas with a stable size (10%), 65 with volume reduction (83%), and only 5 meningiomas with an increased size (7%); minor response in 42 (53%); and major response in 23 (30%). Progression was present in 5 meningiomas (7%). The total tumor control was 93%. The 5-year PFS for the tumor was 92% (95% confidence interval, 77%–98%); the Kaplan-Meier curve is shown in Figure 1.

We also assessed the average of volume reduction every 6 months through volumetry and we observed that, as of month 18, significant reductions were found and, by month 24, the first cases of complete response were seen, which were kept up to the last revision. Between the initial volumetry and the last revision, the size of the lesions showed a statistically significant decrease compared with the initial volumetry ( $P = 0.0001$ ), as shown in Table 3.

### Clinical Response

In 4 patients, the finding was incidental, because they were asymptomatic regarding the meningioma and they were treated with RS without any previous surgery. Before treatment, 71 patients showed symptoms. Of these patients, 32 were treated with RS alone and 39 with surgery before the RS. Symptoms improved in 22 patients (61%) of the group treated with RS alone and 25 patients (64%) of the group with previous surgical management. No changes were present in 14 patients (39%) of the group who received RS alone and in 12 patients (31%) with a surgery background. Symptoms worsened only in 2 patients (5%) with a surgery background. There was no statistically significant difference between both groups.

### Changes by Radiation and Acute and Late Morbidity

Changes induced by radiation were assessed through MRI. Edema was predominant, because it was present in 44 patients (59%) and it was more frequent and had greater volume in the group with previous surgery (30/39, 77%), compared with (14/36, 38%) for

**Table 4.** Volumetric Response Predictors in 75 Patients with Grade I Meningiomas Treated with Radiosurgery (Multivariable Logistic Regression)

Variable	P Value	Relative Risk
Age	0.020	0.95
Volume at 18 months	0.045	0.70
Homogeneity	0.011	15

those treated with RS alone. All patients received steroids before the RS, whether they had a previous surgery background or not. Edema was assessed in T2 sequences and volumetry was performed as well. In patients that showed edema and had a surgery background, the time point between the surgery and RS was 32.4 months on average (median, 11 months; range, 1–180 months).

Of 39 patients with a surgery background, 30 showed edema, 13 (33%) in a period greater than the median and 17 (43%) lower than the median, and this comparison was not different from the statistical viewpoint ( $\chi^2 = 0.41$ ;  $P = 0.75$ ); notwithstanding, if we consider the average of this interval (32.4 months), the difference is marginally significant ( $P = 0.05$ ).

Symptomatic edema after RS appeared in 39 of 75 patients, of whom 28 had a surgery background (71%), compared with only 11/36 (30%) who received only RS ( $\chi^2 = 12.755$ ;  $P = 0.001$ ), which indicates that the surgery background has a significant link with the presence of symptomatic edema (relative risk, 2.35, IC95% 1.38–3.99, odds Ratio 5.78, IC95% 2.14–15.64). No case required hospitalization and only treatment with steroids was administered and led to full resolution of symptoms. No patient needed management with a hyperbaric chamber.

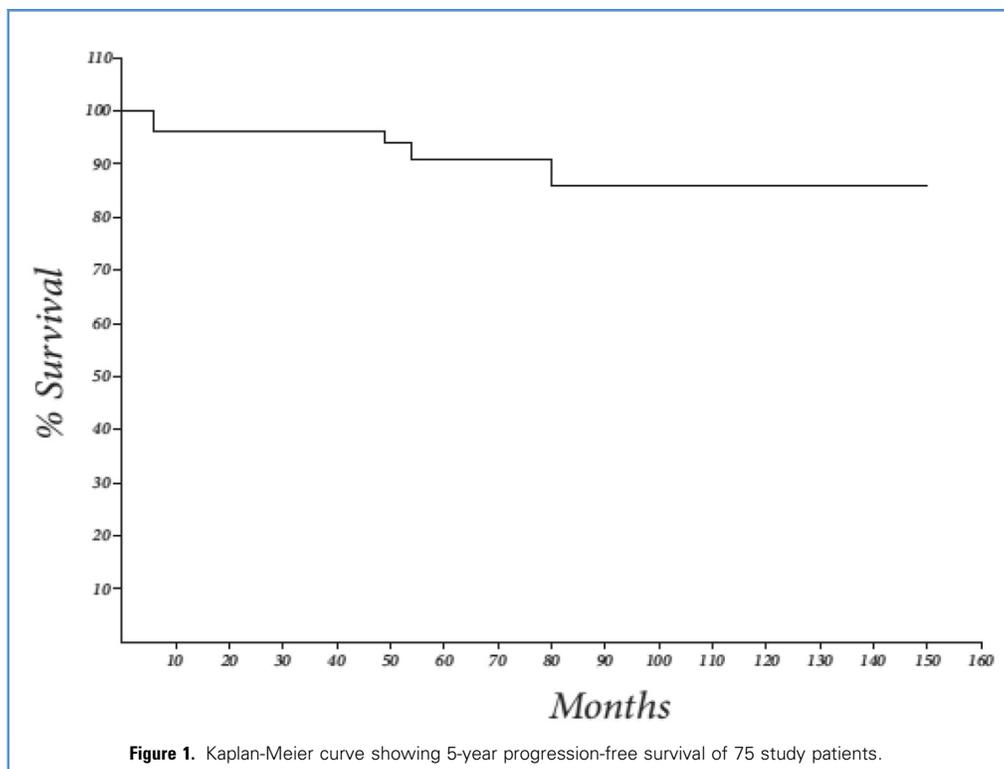
Regarding the size of the tumor, in patients treated with surgery plus RS, the average size was  $4.44 \pm 3.4$  cm<sup>3</sup> compared with those treated with RS alone, in whom the size was  $4.73 \pm 4$  cm<sup>3</sup> when compared using a Student t test ( $P = 0.74$ ).

The volume of tumors located at the base was  $3.32 \pm 3.22$  cm<sup>3</sup> and that for those located at the convexity was  $4.54 \pm 3.50$  cm<sup>3</sup>, which, when compared using a Student t test, did not have a significant difference.

Also, according to the reports of Hoe et al.,<sup>14</sup> tumors >4.2 cm<sup>3</sup> are linked to a greater risk of peritumoral edema after RS; of our patients treated with surgery plus RS, 17 of 39 (43.5%) had a tumor >4.2 cm<sup>3</sup> and 14 of 36 (38.8%) treated with RS alone ( $\chi^2 = 0.17$ ;  $P = 0.75$ ), which indicates that the tumor size did not have a statistical difference between both groups and did not significantly influence the presence of edema after the RS + surgery, as opposed to the report by Hoe et al.

Several investigators have reported that the size of the tumor is a significant factor in the development of edema. We found that volumes >3.43, 4.2, 4.5, 4.7, and 7.1 cm<sup>3</sup> have been reported as significant for the development of edema after RS in patients treated with Gamma Knife radiosurgery (GKRS) (Elekta, Stockholm, Sweden) or LINAC. We studied each of these volumes in our patients and, except for a volume > or <7.1 cm<sup>3</sup> ( $P = 0.05$ ), none had statistical significance.

Regarding the location of meningiomas, the criteria of Zhou et al.<sup>13</sup> were used to determine which meningiomas were located



on the base and which on the convexity; 30 meningiomas were located on the base and 48 on the convexity and the distribution thereof was as follows: 25 on the convexity and 17 on the base for the surgery plus RS group; 13 on the base and 23 on the convexity for the RS alone group. Distribution did not represent a statistical difference ( $\chi^2 = 0.56$ ;  $P = 0.75$ ).

Furthermore, 28 of 48 meningiomas (58.3%) located on the convexity and 17 (56.6%) of those located on the base showed edema, which is not statistically different ( $P = 0.90$ ).

Also, it has been reported that the parasagittal and falx cerebri locations show a significantly greater risk of edema. We studied these locations in our patients and found that 15/23 meningiomas (65.2%) located on the falx cerebri and parasagittal showed edema compared with 35/55 (63.6%) located elsewhere. This difference did not represent a statistical difference ( $P = 0.25$ ;  $\chi^2 = 0.018$ ).

In the group of patients with a surgery background, the preoperative volume of tumors was on average  $19.82 \pm 23.23 \text{ cm}^3$  for those located on the base and  $51.17 \pm 69.67 \text{ cm}^3$  for those located on the convexity, which indicates that convexity tumors were significantly greater than those located on the base ( $P = 0.045$ ; Student t test).

One 68-year old female patient had 2 meningiomas of  $6.08 \text{ cm}^3$  and  $8.1 \text{ cm}^3$ , respectively, treated 8 months apart, both with marginal 18 Gy. The first had 8 conformal static fields and the second had 6 dynamic arcs; after the second RS, the patient showed radionecrosis and significant edema within the first 3 weeks after treatment. She was hospitalized and despite the measures taken against the edema, she died; thus, we considered this to have been a death linked to treatment. One male patient

showed hydrocephaly, which did not require branching, and 2 patients showed mild parenchymatose atrophy with no clinical relevance.

Late morbidity (>6 months after management with RS) was present in 23 patients in the total group (31%) and there were no significant differences between the RS alone or RS plus previous surgery groups. Headache prevailed in 9 patients (12%) and 5 (6.6%) experienced disturbances in a cranial pair. Depression affected 6 patients (8%) (1 patient with RS only and 5 with surgery before the RS) and this group had a statistically significant presence ( $P < 0.01$ ). However, in view of the small number of cases, no risk factors can be defined as linked to the treatment and no psychiatric assessment was performed for any patient before the treatment.

Regarding response-predicting indicators, age, volume at 18 months, and homogeneity were significant in unvaried logistic regression (see Table 4). These 3 indicators lost significance when the multivariate logistic regression was performed.

Considering that age was a response-predicting factor in the univariate logistic regression, we observe that the group <55 years of age had a greater response (reduction of >75% of the initial tumoral volume), which was statistically significant, with  $P < 0.01$  (Table 5). This finding has not been previously reported in the literature and underlines the importance of considering the response with other criteria, as we mentioned in this study, because almost all of studies are based on the assessment of response, considering only the percentage of patients whose lesion progresses and the remaining patients with stable disease.

In the univariate logistic regression for edema-predicting indicators, both age and previous surgical management background

**Table 5.** Relation Between Age and Response in 75 Patients with Meningioma Treated with Radiosurgery

	Volume Tumoral Reduction >75%	Volume Tumoral Reduction <75%
Age <55 years	20	28
Age >55 years	2	25
$\chi^2 = 9.78; P = 0.005.$		

were statistically relevant; nevertheless, in the multivariate logistic regression, only the surgery background prevailed, with  $P = 0.002$ , conferring a risk 5.78 times greater for edema appearance in the group with previous surgery compared with the group of patients with RS only (Table 6). No patient with exclusive radiosurgical management had edema on being diagnosed via imaging, because this is an exclusion criterion for RS during the institution's Tumor Board sessions.

After both the univariate and multivariate logistic regression for progression predicting indicators were performed, none was found to have statistical significance.

Tumor volume before RS for patients who showed a response >75% was  $36.35 \pm 30.2$  and that of patients with tumors with a response >75% was  $42.82 \pm 64.7$  cm<sup>3</sup>, which was not statistically different ( $P = 0.7$ , Student t test). Also, the average of the dose prescribed for each group of patients was  $19.72 \pm 2.4$  Gy; there was a decrease <75% compared with  $20.82 \pm 2.5$  Gy in those who had a response >75%, which was not statistically significant either.

## DISCUSSION

Stereotactic RS is an established and well-accepted therapeutic option for the treatment of intracranial meningiomas,<sup>15</sup> and even when historically the preferred choice was surgical removal, RS was applied preferentially to patients who showed risk from the surgical viewpoint. This is the case for older patients and patients with significant comorbidities, recurrence after an incomplete resectioning, and lesions located in eloquent areas or areas with difficult access.<sup>16</sup> Local control in meningiomas is the primary objective of the treatment and may be defined by stabilization of the tumor without later growth, or late tumor volume regression with either partial or full reduction.<sup>17</sup>

There are several series in the literature that report results on the management of meningiomas with RS, with and without previous surgery, all retrospective, except for 2,<sup>18,19</sup> and by using different technologies in treatment; most patients have been treated with GKRS<sup>19-55</sup> and in a lesser proportion with a LINAC with multi-leaf microcollimator,<sup>56-76</sup> with CyberKnife (CBK) (Accuray, Sunnyvale, California, USA),<sup>77,78</sup> or with protons.<sup>79</sup>

The literature reports 5848 patients treated with GKRS with long-term follow-up up to 2014, with a follow-up average of 62–86 months, marginal dose average of 12–18 Gy and a median PFS of 90%–100% in 5 years, 86%–92% in 10 years, and 83%–91.4% in 20 years,<sup>80</sup> although almost all survival reported is actuarial to 5, 10, or 20 years. Also, these series combine the results of grade

I, II, or III meningiomas and different locations. The best results correspond to grade I meningiomas. Likewise, reported follow-ups are diverse and vary from 1 month up to 284 months (Table 7).

Even when most patients have received treatment with GKRS, the number of patients treated with LINAC constitutes a major proportion of all patients with grade I meningiomas reported in the literature, with an approximate total of 1106 patients, a median follow-up of 46.8 months, median marginal dose of 15.54 Gy, and median PFS of 95% to 2 years, 93.4% to 5 years, 96% to 9 years, and 95.7% to 15 years, which makes results reported with GKRS and LINAC completely comparable regarding control rate and PFS, although with less follow-up time.

This is a retrospective review of this management modality for intracranial meningiomas with a dedicated LINAC 16 years after the beginning of the radioneurosurgery unit of Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez and represents the largest RS series reported in Mexico and a remarkable adherence to follow-up by the patients.

Only WHO grade I meningiomas with and without previous surgery and >24 months of follow-up were included, which is an important criterion to consider because some series reported in the literature have follow-ups of only 1 month.

The factors required for the performance of an adequate RS for grade I meningiomas are adequate patient selection, granting a conformal radiation, and an adequate marginal prescription dose,<sup>21</sup> although the dose-response ratio for meningiomas is poorly characterized.<sup>26</sup> The median marginal prescription dose of 16.2 Gy in our patients is similar to that reported in the literature and within the recent suggestion as an adequate dose for controlling the tumor, decreasing the possibility of recurrences and attaining a low acute and late toxicity rate according to the reports by Kondziolka et al.,<sup>81</sup> and, although it is slightly greater than the dose reported by Pollock et al.,<sup>21</sup> which was 15 Gy, and even closer to the window of between 12 and 16 Gy recommended by Kollová et al.,<sup>82</sup> as a dose, >16 Gy has been linked to a greater percentage of edema after surgery and doses <12 Gy are linked to a lower tumor local control rate.

Compared with previous series, ours includes an intermediate number of patients, compared with large series, such as a German multicenter study<sup>32</sup> and the Pittsburgh series,<sup>41</sup> which has been operating for >18 years as the only center, with approximately 800 patients with grade I meningioma treated with RS based on GKRS.

Compared with reported series in which treatment is administered with a LINAC, our series has a number comparable to that of the others, with an adequate tumor local control rate and scarce acute and late morbidity.

We reviewed all reported treatment series for meningiomas with LINAC by considering only grade I meningiomas and, as shown in Table 8, the number of patients is lower than that reported for patients treated with GKRS; however, it is comparable regarding local control and progression rates attained both with LINAC and GKRS (around 93%), although follow-ups are minor and only 1 reported study with LINAC has a long follow-up (15 years); in general, prescribed doses have decreased in more recent reports and are within a range between 7 and 25 Gy, although it has been reported that an increase in the radiation dose improves the local

**Table 6.** Predictors Variables for Peritumoral Edema After Radiosurgery in 75 Patients with Grade I Meningioma (Multivariable Logistic Regression)

Variable	P Value	Odds Ratio
Age	0.041	1.040
Previous surgery	0.002	5.78 (95% IC, 2.14–15.64)

control rate and survival in patients treated with GKRS for patients with atypical and malign meningiomas; according to Shin et al.,<sup>83</sup> who reported that there are fewer recurrences in patients who receive a marginal dose  $\geq 14$  Gy compared with patients with grade I meningiomas who receive a marginal dose between 10 and 12 Gy; other parametric comparisons between different studies were attempted and comparison was not possible because medians and averages were indistinctly reported.

Our median follow-up is 68 months and the 93% control report is real and not actuarial as shown in other 5-year, 10-year, 15-year, and 20-year series. Only 7% of patients had progression; this percentage is similar to those reported in the literature<sup>8,15,20–25,29,32,80</sup> (see Table 7).

Previous series have reported meningiomas that, without histology (no biopsy) and with diagnosis only through MRI, have been treated with RS, without previous surgery. Flickinger et al.<sup>45</sup> and Jang et al.<sup>33</sup> reported patients treated with RS alone, identifying 847 patients with a median follow-up of 29 and 37 months, respectively. In our series, 46% of patients have been managed without previous biopsy. This result is in an intermediate place among the percentages of patients treated with RS only, according to descriptions from other studies. This finding shows an increase in trust by the neurosurgery group in our institute regarding the management of intracranial meningiomas with RS alone.

None of our patients with progression has required management after RS. Kondziolka et al.<sup>41</sup> reported a 2.3% error in the appreciation of meningiomas when they are assessed only with resonance and, when patients are taken to surgery because of their progress, they are reported as WHO grade II or III.

We also analyzed a review of series from the literature that report edema after surgery with GKRS, LINAC, or CBK. There are 42 previous series that report edema in patients treated with RS for meningioma (Table 9). Our result regarding the edema percentage (52%) found lies within ranges reported in other series and within the dose range. Other series (Ramsey et al.,<sup>49</sup> Vermeulen et al.,<sup>50</sup> Kondziolka et al.,<sup>52</sup> and Nakamura et al.<sup>53</sup>) reported between 10% and 39% edema presence, although these reports suppress patients who had edema on diagnosis; an important criterion for our group is that, if patients show edema on diagnosis, they are taken to surgery from the beginning. As has been commented in the Results section, the greatest incidence of edema in our series was in patients with previous surgery, similar to reports by Pollock et al.,<sup>21</sup> Jang et al.,<sup>33</sup> and Starke et al.<sup>87</sup> in patients treated with GKRS. All MRIs before surgical management were not retrieved to assess the magnitude of preoperative edema. We considered that the high frequency of edema after RS in our patients was a result of the dose used, because, although in the univariate and multivariate analysis, the prescribed marginal dose did not reach statistical significance, more of our patients received doses greater than marginal 16 Gy and which, according to some investigators, is a significant factor linked to the development of edema after RS.<sup>14</sup>

If the average percentage for edema is reported according to technique used, we may observe that, with GKRS, the average edema was 19.16%, with a range of 1%–86%; with LINAC, the average was 15.65%, with a range of 2%–51%; with CBK, the average was 8.53%, with a range of 2.9%–14.7%; this finding does not represent a statistically significant difference ( $P = 0.27$ ) and shows a great variability in the presence of edema reported in different series and in factors that have been involved, such as tumor volume,<sup>31,32,36,39,52,77,91</sup> marginal prescription dose,<sup>31,37,42,50,54,82</sup> histology,<sup>91</sup> the location of convexity,<sup>22,31,32,38,46,50,53,92</sup> conformity index,<sup>34</sup> brain-tumor interface,<sup>39,93</sup> and vascular endothelial growth factor.<sup>94–97</sup> Hoe et al.<sup>14</sup> reported on 320 patients treated with GKRS for incidental meningiomas and stated that the presence of peritumoral edema before RS and previous surgical treatment are risk factors of edema after RS. Jang et al.<sup>33</sup> reported on 628 with meningiomas diagnosed only with RM and treated with GKRS and found that patients

**Table 7.** Comparison Between Instituto Nacional de Neurología y Neurocirugía Series and Previous Gamma Knife Radiosurgery Series

Reference	N	Follow-Up (months)	No Histology	Dose (Gy)	PFS $\geq 5$ years (%)
Santacroce et al., 2012 <sup>32</sup>	3678	63	64	14	92.5
Kondziolka et al., 2008 <sup>41</sup>	873	48	58	14	91 a 97
Flickinger et al., 2003 <sup>45</sup>	219	29	100	14	93
Di Biase et al., 2004 <sup>44</sup>	137	54	62	14	86.2
Nicolato et al., 2002 <sup>48</sup>	111	48	50	15	96
Roche et al., 2000 <sup>47</sup>	80	31	63	14	93
Pollock et al., 2012 <sup>21</sup>	62	64	46	17.7	95
Chuang et al., 2004 <sup>65</sup>	43	75	48	16	90
Instituto Nacional de Neurología y Neurocirugía	78	56	46	16	92

**Table 8.** Radiosurgery Series of Grade I Meningiomas with Linear Accelerator–Based Treatment

Reference	N	Months of Follow-Up Median or Mean (Range)	Control rate %	Marginal Dose (Gy) Median or Mean (Range)	Progression-Free Survival (years) %	Localization
Naoui et al., 1996 <sup>56</sup>	2		83			Several
Golanov et al., 2010 <sup>58</sup>	4	18.4 (6–42) X	97.5	16.25 X		Groove medium
Zamorano et al., 1997 <sup>59</sup>	7	33 (12–48) Md	88			Several
Biswas et al., 2003 <sup>60</sup>	12	36 (12–43) X	100	12.8 (8–18) X		Several
Chang et al., 1998 <sup>61</sup>	24	45.6 (19–80) X	100 (A)2	17.7 (14–20) X		Cavernous sinus
Abdelaziz et al., 2011 <sup>62</sup>	29	60 (36–70) Md	93.3	10.9 (8–14) Md	93.3 (A)	Several
De Salles et al., 2001 <sup>63</sup>	34		90	12–22		Skull base
Spiegelmann et al., 2002 <sup>64</sup>	42	38 X	97.5	14 X		Cavernous sinus
Chuang et al., 2004 <sup>65</sup>	43	74.5 Md	89.7 (A)7	16 X	80.2 (7 years)	Several
Matsuo et al., 2009 <sup>57</sup>	53					Several
Chang and Adler, 1997 <sup>66</sup>	55	48.4 (17–81) X	98 (A)2	18.3 (12–25) X		Skull base
Deinsberger and Tidstrand, 2005 <sup>67</sup>	55	66 (9–96) Md	95.8 (5)	14.6 (11–18) Md		Skull base
Villavicencio et al., 2001 <sup>68</sup>	56	26 (6–66) Md	95	15 (12–18.5) X	95 (A) 2 years	Skull base
Kimball et al., 2009 <sup>69</sup>	56	50 Md	98 (A)10			Cavernous sinus
Shafron et al., 1999 <sup>70</sup>	70	23 Md	100	12.7 (10–20) X		Several
Hadelsberg et al., 2015 <sup>96</sup>	74	49 (12–144) X	90.6 (A)4	13 (10–16) Md		Parasagittal
El-Madjoub et al., 2012 <sup>72</sup>	78	79.7 (24.2–109.1) Md		16 X	96 (A) 9 years	Several
Torres et al., 2003 <sup>73</sup>	79	40 X	90	15.6 (12–22.85) X		Several
Diconglan et al., 2013 <sup>71</sup>	79	53 (9–112) Md	89.7	13 (10–16) Md		Several
Spiegelmann et al., 2010 <sup>74</sup>	102	67 (12–180) X	98 (A)5	13.5 (12–17.5)X		Cavernous sinus
Hakim et al., 1998 <sup>75</sup>	106	31 (1.2–79.8) Md	89.3 (A)5	15 (9–20) Md	5 (A)	Several
El-Khatib et al., 2015 <sup>76</sup>	148	151 (61–259) X	93.6 (15)	12 (7–20) Md	89 (15 years)	Several
Instituto Nacional de Neurología y Neurocirugía	75	68 (35–120) Md	93	16.2 (12–20.8) Md	92 (5 years)	Several
Total	1106	46.8 (1.2–259)	93.3 (76.4–100)	15.54 (7–25)		

X, mean; Md, median; (A), actuarial.

with previous surgery and peritumoral edema had lower PFS. These findings are contrary to a report by Novotny et al.,<sup>42</sup> who observed that patients with no surgery background had significantly more edema after RS with GKRS, although their study included patients with typical, atypical, and malign meningiomas.

Sheehan et al.<sup>31</sup> reported a multicenter study of meningiomas with parasagittal and parafalcine locations with 45.3% edema after RS. Also, the edema and RS on meningioma Pittsburgh series<sup>22</sup> reported that 16% of patients showed edema linked to the parasagittal location; notwithstanding the average percentage (19.05%) reported in all series in which patients with edema in this location were exclusively treated, the edema percentage does not seem to be significantly greater than that reported for other >10 cm<sup>3</sup>, sinus venosus compression, pial input,<sup>95</sup> and

invasion depth of meningiomas to the dura and presence of blood vessels with increase in their permeability within the meningioma tissue.<sup>98</sup> Our analysis did not find a significant difference of edema through meningioma topography. However, the sum of parasagittal and falx cerebri sites amounts to 33% of patients who showed edema.

We show the results of response of meningiomas to RS by volumetry reduction percentage. A recent revision suggests that the volumetry follow-up of tumor response to RS is adequate for measuring the response and that it should be reported in all studies. Also, this measure is absent of in most studies,<sup>99</sup> and none of the reported studies has a uniform manner for reporting tumor reduction; some investigators used measures in only 2 dimensions and others reported volumetry. Also, methods for determining tumor volume are variable and we

**Table 9.** Comparison Between Previous Series with Peritumoral Edema Report After Radiosurgery

Reference	N	Follow-Up (months)	Median Dose (Gy) or (Range)	Edema (%)	Technology	Localization	Previous Surgery
Ganz et al., 1996 <sup>54</sup>	34	15	(12–25)	86	GKRS	Several	NR
Nakamura et al., 1996 <sup>53</sup>	48	12	15	25	GKRS	Several	NR
Han et al., 2017 <sup>29</sup>	42	57.8 median	12 (8–14)	11.9	GKRS	Several	14
Kondziolka et al., 1998 <sup>52</sup>	203	42	15	16	GKRS	Parasagittal	137
Ramsey et al., 2002 <sup>49</sup>	23	17	14	39	NR	NR	NR
Vermeulen et al., 1999 <sup>50</sup>	95	2.3	(8–20)	12	GKRS	Several	NR
Hoe et al., 2015 <sup>14</sup>	320	48	13	15.3	GKRS	Several	0
Jang et al., 2015 <sup>33</sup>	628	37	13.9	15	GKRS	Several	131
Hasegawa et al., 2011 <sup>38</sup>	112	72	16	23.2	GKRS	Convexity	61
Hsieh et al., 2010 <sup>78</sup>	68		18	2.9	CBK	Supratentorial	
Unger et al., 2012 <sup>36</sup>	160	21	15	8	GKRS/CBK	Several	84
Patil et al., 2008 <sup>89</sup>	102	20.9	18	14.7	CBK	Supratentorial	
Pollock et al., 2012 <sup>21</sup>	416		16	11	GKRS	Several	164
Sheehan et al., 2015 <sup>31</sup>	212	19.6	14	45.3	GKRS	Parasagittal	127
Starke et al., 2015 <sup>87</sup>	75	6		5.3	GKRS	Skull base	45
Lee et al., 2016 <sup>15</sup>	113	12	13.3	6.1	GKRS	Several	28
Kuhn et al., 2014 <sup>88</sup>	194			21	GKRS	Several	
Cai et al., 2010 <sup>39</sup>	163	21	13.6	24.7	GKRS	Several	64
Chang et al., 2003 <sup>46</sup>	179	37.3	15.1	23.6	GKRS	Several	70
Kobayashi et al., 2001 <sup>90</sup>	87	30	14.5	10.3	GKRS	Several	34
Tanaka et al., 1996 <sup>55</sup>	33	26.5	15.1	12.1	GKRS	Several	23
Singh et al., 2000 <sup>91</sup>	77	122	(10–15)	11.6	GKRS	Several	49
Kollová et al., 2007 <sup>82</sup>	331	60	12.55	15.4	GKRS	Several	
Mansouri et al., 2015 <sup>34</sup>	75	36.2	13	18.7	GKRS	Several	21
Bitzer et al., 1997 <sup>92</sup>	175			61.1	GKRS	Several	179
Pan et al., 1998 <sup>51</sup>	80	21	12–20	31	GKRS	Several	
Sethi et al., 2015 <sup>26</sup>	88	25	14	5	GKRS	Several	46
Kondziolka et al., 2009 <sup>40</sup>	109		14.2	5	GKRS	Convexity	55
Kondziolka et al., 2008 <sup>41</sup>	800			4	GKRS	Several	392
Kreil et al., 2005 <sup>43</sup>	200	95	12	1	GKRS	Several	99
Park et al., 2014 <sup>35</sup>	74	40	13	14	GKRS	Cerebellopontine angle	
Ding et al., 2013 <sup>93</sup>	65	56.6	15	8.2	GKRS	Parasagittal	
Lee et al., 2012 <sup>37</sup>	64	13.4	19.1	28.1	GKRS	Several	14
Novotny et al., 2006 <sup>42</sup>	368	51		15.2	GKRS	Several	
Abdelaziz et al., 2011 <sup>62</sup>	29	36	11	6.7	LINAC	Several	7
Egenhart et al., 1990 <sup>84</sup>	17	40	29	34	LINAC	Several	
El-Kathib et al., 2015 <sup>76</sup>	148	150	12	2	LINAC	Several	80
Dincoglan et al., 2013 <sup>71</sup>	79	53	13		LINAC	Several	

GKRS, Gamma Knife radiosurgery; NR, not reported; CBK, CyberKnife; LINAC, linear accelerator.

Continues

Table 9. Continued

Reference	N	Follow-Up (months)	Median Dose (Gy) or (Range)	Edema (%)	Technology	Localization	Previous Surgery
Torres et al., 2003 <sup>73</sup>	79	40	15	5	LINAC	Several	84
Shafron et al., 1999 <sup>70</sup>	70	23	12.7	2.8	LINAC	Several	32
Kan et al., 2007 <sup>85</sup>	18		13–15	17	LINAC	Several	14
Hadelsberg et al., 2015 <sup>86</sup>	74	49	13	6.7	LINAC	Parasagittal	61
Instituto Nacional de Neurología y Neurocirugía	75	68	16.4	52	LINAC	Several	39

GKRS, Gamma Knife radiosurgery; NR, not reported; CBK, CyberKnife; LINAC, linear accelerator.

chose the method integrated in the Brainlab iPlan planning system because it allows comparison of tumoral volume with total brain volume; also, most investigators consider the criterion of a reduction of  $\pm 10\%$  as a stable response, some consider  $\pm 15\%$ , and others  $\pm 20\%$ <sup>25,46</sup> (e.g., El-Khatib et al.<sup>76</sup> used criteria from McDonald that were for gliomas). There is a link between having an age  $< 55$  years and the possibility of having a response  $> 75\%$ . This link is difficult to prove with other studies because of the absence of this measure and also because, in many previous studies, atypical meningiomas are reported together with grade I and our study excluded atypical meningiomas. Also, there are no consensus criteria for measuring response and we await a report from the RANO (Response Assessment Neuro Oncology) Group Sub-Committee on this matter.<sup>100</sup> Our proposal has the advantage of being similar to widely used criteria in oncology that allow comparison of the results obtained by different research groups.

Nineteen percent of patients in our series showed a response between 76% and 90% and, in 10% of patients, a response between 91% and 100% was observed (i.e., almost one third of our patients showed a greater response); it is relevant to assess whether this finding is related to some molecular factor already described, such as the amount of receptors to VEGF,<sup>96</sup> MIB-1,<sup>101</sup> the  $\beta$  transforming factor expression,<sup>102</sup> or mutations in PI3K<sup>103</sup>; we were not able to assess these data in this study, because it has been reported that their presence has influence on the response to RS. Volumetries were performed by 2 physicians (1 neurosurgeon and 1 radio-oncologist) who were not involved in treatments and assessed by another neurosurgeon to suppress the dependent operator error.

Being older or younger than 55 years was a determining factor for responses  $> 75\%$ , which had not been reported before in the literature. Also, even when several reports found age to be a response-predicting factor, ages were diverse, although if we consider that Zhou et al.<sup>13</sup> reported that younger patients have greater risk of grade II or III lesion, it is possible to consider that, if the different studies that report on age are revised, it

would be feasible to find a link between degree of histology and older age. Domingues et al.<sup>104</sup> also report that being younger than 55 years is an adverse factor for attaining 5-year PFS.

Based on our findings in our patients and our revision in the literature, we consider that collective decision making is advisable when deciding the conduct to follow with each patient; RS is an unquestionable option in patients with small tumors ( $< 3$  cm) located on the base or in eloquent regions or, in cases of residual tumors after the surgery, advisable in patients with meningiomas located on the convexity and that, notwithstanding their tumoral volume, do not show edema before any treatment, because several studies have shown that the presence of edema before RS is a determining factor for the presence of edema after RS notwithstanding whether RS is granted with a background of microsurgery or none; in addition the risk of second neoplasias or radio-induced tumors in patients subject to long-term radiation is minimal and independent of their age.<sup>105,106</sup>

The limitations to our study are its retrospective nature, the small number of patients, the single-center experience, lack of pathologic diagnosis in many patients, and a follow-up that barely exceeds 5 years in a disease that is benign in essence.

## CONCLUSIONS

The meningioma RS control response rate, either with or without previous surgical management, shows that PFS to the median follow-up by 68 months is 93%, with 7% accounting for meningiomas with progression and average marginal doses of 16 Gy, which is in agreement with previously reported series.

Age older than 55 years was found to be a determining factor for a response  $> 75\%$ .

Edema is the main morbidity and the surgery background before RS was the only prognostic indicator of edema after RS; a risk of 5.78 times is thus conferred.

After a univariate and multivariate analysis, no statistically significant factors were found for predicting a final response or progression.

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