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Clinical Investigation

Stereotactic radiosurgery as a salvage treatment option for atypical meningiomas previously submitted to surgical resection

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Background: Surgery is the initial treatment for atypical meningiomas (AM), but in cases of recurrence, options become more limited. We present our results from salvage treatment with stereotactic radiosurgery (SRS) in previously surgically treated patients. *Methods*: Sixteen patients treated between 1993 and 2007 were retrospectively reviewed. The mean follow-up was of 66.5 months. Most of the patients (81.3%) presented a single tumor nodule, while 3 presented multicentric disease (18.7%). Lesion volumes varied from 0.8 to 12 cm^3 (mean: 6.1 cm^3). A dose of 12 to 16 Gy was prescribed according to isodose curves from 50 to 90%. *Results*: After SRS, 3 of the patients (18.8%) presented with tumor volume reduction, 7 (43.8%) remained stable, and 6 patients presented with tumor progression. The Kaplan-Maier-estimated progression-free survival (PFS) and overall survival (OS) were 70.3% and 87.1% at 5 years and 44% and 54.4% at 10 years. Age, sex, site and tumor volume were not significantly associated with the prognosis. Patients presenting with multicentric disease presented a poorer prognosis, although without statistical significance ($p = 0.14$). *Conclusions*: SRS provided an effective and safe treatment for this group of patients with recurrent NBM. Patients who present with multicentric disease will probably fare more poorly.

Key words: atypical – meningiomas – stereotactic radiosurgery

INTRODUCTION

Atypical meningiomas (AM), unlike their benign counterparts, are slightly more predominant in males and are characterized by aggressive behavior. Recurrence rates vary between 29 and 52%, depending on variables such as the extension of the resection or the use adjuvant of treatment [1-6].

When AM recur, they can be particularly difficult to manage. Scar formations can make additional surgeries challenging, and complete tumor resection is difficult to achieve [7]. To date, no systemic approaches have been effective, leaving radiation therapy [8] and stereotactic radiosurgery (SRS) as possible treatment options. SRS has the advantage of a short treatment course; however, it should be avoided with larger lesions due to the elevated risk of marginal failure [6,8,9].

There are few published studies focusing exclusively on recurrent AM patients. Data usually include patients treated in the adjuvant setting, an appreciably different group that rarely faces management limitations arising from previous treatments. Additionally, the available results are difficult to interpret because pathological classification was highly imprecise before 2000 and has changed often since that time.

Since 2000, in an attempt to increase the accuracy of categorization, the diagnosis of atypical meningioma has been based on a combination of defined histological

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features, including increased mitotic activity, hypercellularity, eosinophilic macronucleoli, sheet-like growth, and small cell collections. On the other hand, the presence of frank malignancy would be sufficient to diagnose anaplastic meningioma [6,10-12]. Due to the rarity of the disease and the imprecision of the available data, the optimal management of recurrent AM remains undefined. We present here our results from salvage treatment with stereotactic radiosurgery (SRS) in previously surgically treated patients based on the longest follow-up period reported to date.

PATIENTS AND METHODS

The radiosurgical database of Hospital San Francisco/ Madrid, Spain was reviewed. From 1993 to 2007, 18 patients with recurrent AM, previously submitted to at least one open surgery, were sent to our institution to be considered for SRS. Patients with less than 6 months of follow-up (n=2) were excluded. The remaining 16 patients' files were retrospectively reviewed. All cases were re-evaluated at our institution to confirm the histopathological diagnosis according to the 2000 World Health Organization (WHO) classification [11].

There was a male predominance (69%). Ages varied from 16 to 76 years (mean: 48.7 years). The most frequent recurrent tumor sites were the convexity of the skull and the parasagittal area (40 and 35% respectively). The remaining 25% were located at the skull base. Five patients had received another surgical resection before being considered for SRS.

Adjuvant Treatment

Four patients received adjuvant radiotherapy at other institutions. In all cases, fractionated stereotactic radiotherapy (FSRT) was used, and the dose varied from 54 to 65 Gy (1.8 to 2 Gy/day). Two received the treatment after two consecutive partial resections and subsequent progression; the third received treatment after a first partial resection; and the fourth was the only patient who received adjuvant radiotherapy after an initial radical surgery. None had previously received SRS. All were men, and all presented with recurrence that led to SRS after a mean of 22.5 months (range: 8.4 to 30.1). No patients received systemic treatment.

Among the others not irradiated patients, five were submitted to a second surgery after first tumor progression, and the remaining eight were kept under close surveillance, once a macroscopic complete surgical resection was achieved.

Recurrences Leading to SRS

The recurrences occurred an average of 29.5 months after the first surgery (range: 6.3 to 116.6). At the time of recurrence, most of the patients presented with a single tumor nodule (81.2%), whereas 3 presented multicentric disease (18.8%). Lesion volumes varied from 0.8 to 12 cm^3 (mean: 6.1 cm^3). A total of 20 lesions were treated. The most frequent symptom leading to the diagnosis of recurrence was epileptic seizures (7 patients), followed by varying degrees of hemiparesia (5 patients). All of the patients' characteristics are summarized in Table 1.

In all cases, SRS was administered using a linear accelerator with a high-precision positioning system and mechanical fixation of the tertiary collimator (SRS 200; University of Florida, Gainesville, FL) with 6-MV photons. To locate the lesion, magnetic

Table 1. Patient characteristics

Sex	
Male	11 (69%)
Female	5 (31%)
Age (mean: 48.7 year)	
Younger than 50 years	8 (50%)
50 years or older	8 (50%)
Tumor site	
Convexity of the skull	8 (40%)
Parasagittal region	7 (35%)
Skull base	5 (25%)
Tumor volume (medium 5.6 cm^3)	
0.8 – 5 cm^3	8 (40%)
5.1 – 8 cm^3	7 (35%)
8.1 – 12 cm^3	5 (25%)
Number of nodules	
1	13 (81.3%)
2	2 (12.5%)
3	1 (6.3%)
Second surgery before SRS	
Yes	5 (31.3%)
No	11 (68.6%)
Previous radiotherapy	
Yes	4 (25%)
No	12 (75%)

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resonance images (MRI) were obtained, after which a local anesthetic was administered and the stereotactic frame was placed for the planning CT phase. An image fusion program was used to delimit the target volume. Three-dimensional treatment planning was used in all cases, although different planning units were applied throughout the study period (Philips SRS 200, Philips, Madison, WI; Brain Lab, Brain Lab, Feldkirchen, Germany; Plato-Nucletron, Nucletron, Veenendaal, Netherlands and ERGO-3D Line, 3D-Line Medical Systems, Milano, Italy).

Dose planning was used to conform as closely as possibly to the enhancing tumor. A mean dose of 14.1 Gy (range 12–16 Gy), median 14 Gy, was prescribed according to isodose curves from 50 to 90%, mean 83,8%, median 90% .The number of collimators used varied from 1 to 3: 1 was used in 5 cases, 2 in 11 cases, and 3 in 4 cases.

After SRS, all patients received prophylactic treatment with dexamethasone and remained in the hospital for 24 h to prevent any early complications. Tumor size before and after SRS was assessed by measuring the contrast-enhanced margins in the three standard MRI dimensions, and the volume was calculated based on the assumption that an ellipsoid would be a reasonable representation of the lesion. The dura tail was not considered in this measurement. Follow-up MRI, with and without gadolinium enhancement, was conducted after 3, 6 and 12 months and yearly thereafter. The mean follow-up was 66.5 months (range: 8.4 to 170.1 months).

Statistical Analysis

Progression-free survival (PFS) was calculated based on the amount of time from the procedure (SRS) until recurrence, which was diagnosed if a regrowth was detected on a follow-up MRI. Overall survival (OS) was calculated from the procedure (SRS) until death or last follow-up. To analyze the global result of survival, we also calculated the OS considering the period between the first surgery and the last follow-up, but no statistical evaluations were based on this period of surveillance.

To analyze factors correlating with PFS and OS, the following parameters were assessed: age (defined as the age of the patient at the time of SRS), sex, site, tumor volume and number of tumor nodules (single versus multicentric disease). To study the tumor volume, we arbitrarily divided the patients into two groups: those with tumors smaller than 5 cm^3 (mean: 2.3 cm^3) and those with larger lesions (mean: 7.8 cm^3). Univariate and multivariate analysis were performed for both PFS and OS. The estimate of the cumulative surviving proportion was based on Kaplan-Meier procedures [13]. The survival comparison between groups was performed using the log-rank test. Multivariate analysis was performed using the Cox model. The SPSS version 12.0 was used to analyze the results.

RESULTS

After SRS, 3 patients (18.8%) presented tumor volume reduction (one complete response), 7 (43.6%) remained stable, and 6 presented tumor progression. Two patients (11.8%), one from the stable disease group and the other from the progressive disease group, developed new lesions elsewhere. Four deaths were recorded, all related to the progression of the disease. The Kaplan-Meier estimated PFS was 70.3% at 5 years and 44% at 10 years. Five- and ten-year OS rates were 87.1% and 54.4%, respectively (Figure 1).

Among the 6 patients who presented with local failure after SRS, 3 were submitted to another surgery, and 1 was alive at the end of a 58.1-month follow-up. The other three were sent to palliative care.

Neither age, sex, site nor tumor volume presented significant associations with prognosis. No difference was seen in PFS or OS, neither on univariate nor on multivariate analysis. Patients with multicentric disease presented a poorer prognosis when compared with patients presenting with one lesion at recurrence, although without reaching statistical significance (p=0.14) (Figure 2), result that was maintained after multivariate analysis (p=0.13).

If the date of the initial surgery is considered the beginning of the follow-up, the final OS results would be 87.5% at 5 years and 75% at 10 years (Figure 3). No relevant toxicity was described after SRS.

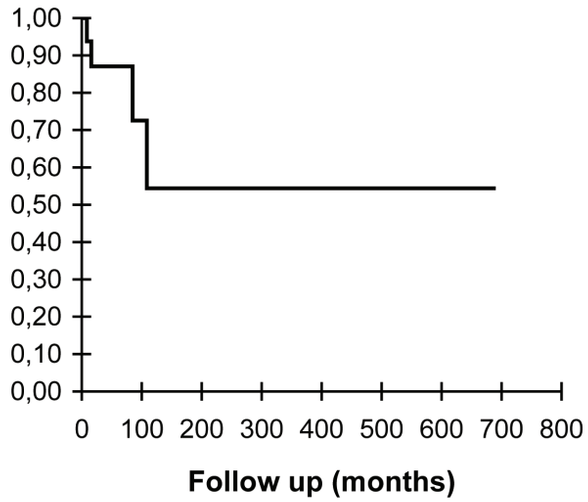

Figure 1. OS of patients with AM after SRS.

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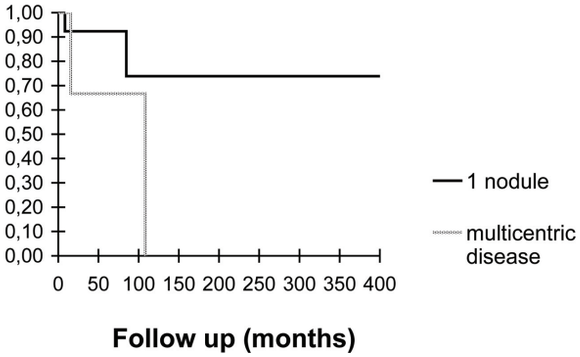

Figure 2. OS according to the number of meningioma nodules (single versus multicentric disease) (p=0.14).

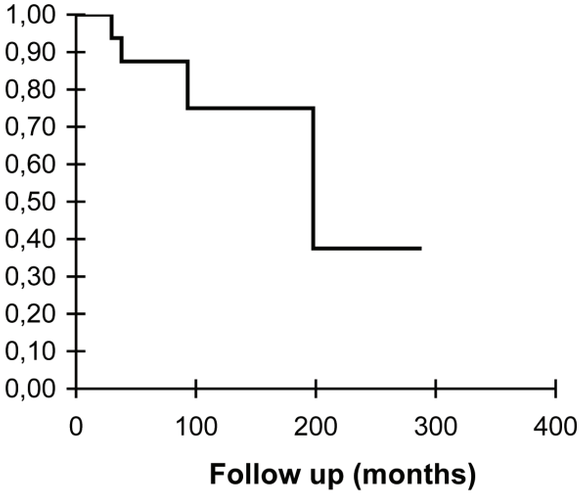

Figure 3. OS of patients with AM after the first surgery

DISCUSSION

The results presented here show that SRS was an efficient and safe treatment for this group of patients with recurrent AM. Multicentric disease remains a dilemma, and finding alternative techniques for its management should be prioritized. Our results illustrate the importance of a long surveillance, as deaths from progressive disease were still reported 5 years after SRS.

Pathology

Before discussing the results, an important observation must be made about the histopathologic diagnosis of non-benign meningiomas. In 2000, the WHO classification [11] underwent substantial re-evaluation based on the clinicopathological series from the Mayo Clinic [10,14]. Prior to this publication, the histological definition of atypical and malignant tumors was very imprecise [15-17]. This revision primarily resulted in some tumors previously diagnosed as benign meningioma being upgraded to the atypical category [12,16,18], which may explain the subsequent increase in the NBM incidence [17].

The 2007 WHO classification was almost identical to the 2000 classification [19], although some pathologists had proposed broadening the definition of atypical tumors by adding brain invasion as a complementary criteria [12,20]. Because patients with brain invasion were often classified as Grade III in accordance with the 2000 classification, we decided to maintain this classification, which has been used since we began collecting data (WHO 2000). Our data would not have been affected because our only patient with a Grade III tumor was classified as anaplasic because of manifested malignancy.

Nevertheless, significant interobserver variability remains a relevant clinical problem in NBM diagnosis because associations between grade and clinical behavior are still imperfect [17]. Furthermore, treatment effects can induce potential errors in grading. For example: pre-operatory embolization, used in some institutions to minimize intraoperative bleeding, induces some histological changes, including necrosis, macronucleoli and an increasing number of mitotic figures that may cause the tumor to be overgraded. Previous radiotherapy can lead to similar mistakes because it can also induce necrosis and atypia [22-24]. Good communication between the surgical team and pathology is of utmost importance for the correct classification of these tumors.

The volume

Matozzo et al. show a 5-year PFS of 70% [25], an outcome that is slightly better than the one presented in our study (65.9%) (Table 2). The authors reported a mean tumor volume of 2.2 cm^3, much lower then the values presented by our patients. If we consider only our group with smaller lesions (< 5 cm^3), the bloc for which we found a similar mean volume (also 2.3 cm^3), our results are slightly better (PFS of 80% in 5 years). We emphasize that no significant differences in outcome were detected among our patients related to lesion volume. However, the low number of cases is a possible reason we did not find the correlation between volume and prognosis that was proposed by other authors [7,9,20]. It is also important to point out that volumes, in this series, were estimated based on an assumption that an ellipsoid would reasonably represent the lesion, a supposition that may, sometimes, be imprecise, making it difficult to rigorously evaluate this variable. The other series were not clear about the method that was used for volume calculations.

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Table 2. Studies of patients with recurrent atypical/anaplasic meningiomas treated with radiotherapy (only results specifically referring to recurrent tumors were considered):

Author (year)	Tech	Pats	Post-op RT	Mean vol (cm^3)	Mean dosage (SRS)	PFS 5 y	PFS 10 y	OS 5 y	OS 10 y	F/up	Com
Ojemann (2000)	SRS	19	19	8.98	16 Gy	34%	–	–	–	118.6 wks	–
Ware (2004)	Brachy	22	22	23.75	N/A	10%	–	–	–	37.2 m	33%
Kano (2007)	SRS	12 (10 GII)		4.4	< 20 Gy > 20 Gy	29.4% 63.1%	– –	80,8%	– –	43.4 m	17%
Mattozo (2007)	SRS	11 (GII)	3	2.2	* 15,5 Gy	70%	–	–	–	42 m	0%
Aghi (2009)	SRS/ FSRT	30 (16 SRS)	0	4.4 (SRS)	18 Gy	–	–	86%**	69%**	39 m	–
This study (2010)	SRS	17	4	5.3	14 Gy	65.9%	35.2%	81.6%	43.5%	64.8 m	0%

Tech: technique used; F/up: follow-up; wks: weeks; m: months; Com: complications reported; SRS: stereotactic radiosurgery; Brachy: brachytherapy; FSRT: fractionated stereotactic radiotherapy; G: tumor grade; N/A: not applicable; -: not reported; *: median dose; **: disease-specific survival

We understand that, as an institution to where patients are referred specifically for SRS, there will be a considerable selection bias towards smaller lesions because larger tumors are referred for other kinds of treatment, elsewhere. Kano et al., after treating 12 patients with a mean tumor volume of 4.4 cm^3, did not find a relationship between the tumor volume and PFS. However, the volume range was not large enough (0.29 to 18 cm^3), and a selection bias could also not be excluded [6]. Aghi et al. reported 30 recurrences among 108 patients with previously surgically treated atypical meningioma. One of the important eligibility criteria for treatment was tumor volume, and only patients with smaller lesions (mean: 4.4 cm^3) were referred to SRS. They presented 5-year results very similar to ours but with better survival after 10 years [20]. One possible explanation for this advantage may be the fact that those results refer to patients with one recurrence after an initial, complete tumor resection, a subgroup that may have a better prognosis. Those patients did not undergo previous treatments other than initial surgery. Our study includes patients in a more advanced stage of their treatment, and almost half of them were submitted to successive surgical resections or previous radiotherapy.

The most relevant limitation of SRS in the treatment of meningiomas in general is tumor volume because a high dose of radiation is delivered in one fraction and the proximity to normal structures can be limiting [7,9,26]. Moreover, in AM treatment, its invasive tendency increases the risk of marginal failure, which must be considered as another relevant factor [5,8]. We understand that it might be unsafe to treat larger lesions and those that fit the previously reported size limit of 8 cm^3 [9] but have a deficient target coverage because of proximity to dose-limiting structures [26-28]. In such situations, other techniques should probably be priorized [7,29,30].

In fact, we have treated some patients presenting with tumors considered large for SRS, and although there may still be a selection bias, about 30% of our study included lesions > 8 cm^3. Our good results in this group, unlike those in the study by Ojemann et al., may be explained by the fact that those patients had larger tumors (mean: 7.35 cm^3, range: 0.59 to 35 cm^3). When the sample was split in two according to the 8-cm^3 limit, the group with larger lesions presented worse prognoses [9]. Our results, on the other hand, open the possibility that the safe limit for SRS may be a little wider, despite the small number of patients treated under these circumstances.

The doses

Mattoso et al. reported no local failures in patients with atypical tumors receiving between 12 and 14 Gy and one failure in a patient who received 16 Gy. This fact led them to declare that higher doses may not be nec-

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essary to treat recurring GII meningiomas [25]. Alternatively, Kano et al. presented a clear dose-response effect in which patients who received more than 20 Gy presented significantly better PFS. The problem is that the results for the higher-dose group are very similar to those presented by other authors for their whole series (including our cases) using lower doses (Table 2). Kano et al. note a clear selection bias in their patients because the ones who received the lower doses were the ones who had the deepest tumors, and their dose prescriptions were restricted because of dose-limiting organs. Perhaps the lower dose was not the sole cause of the poorer results; the results may instead be related to a more difficult site that jeopardized the treatment coverage or the fact that those patients had received previous adjuvant radiotherapy, thus selecting for more-resistant tumors [6].

Multicentricity

Three of our patients presented with recurrences of more then one nodule of meningioma. Those were, in fact, false local recurrences because at least one of the new growing lesions was contiguous to, but independent from, the attachment surface of the primary meningioma. They were actually new primary lesions originating from multicentric tumor foci in the contiguous dura mater [31]. Multicentric disease may occur spontaneously or in association in Neurofibromatosis Type I. It is known that recurring lesions have an increased tendency toward multicentricity, and these lesions also have a higher tendency toward local failure [4]. Because of these characteristics, it seems plausible that those patients present a worse survival rate, although we were unable to demonstrate a significant difference, perhaps because of the low number of patients. We believe that SRS is an unsatisfactory treatment strategy for this group of patients.

Limitations and future research

This study has the evident limitations of a uni-institutional retrospective study of cases collected after a long period of time. Despite the rarity of the disease, we treated a relatively small number of patients, which could impair the reliability of our conclusions. We also note the selection bias inherent in a study from an institution that receives patients specifically for SRS; namely, the patients we receive have usually undergone previous evaluations by different groups of neurosurgeons, with different and variable criteria.

A multicenter trial would be required to prospectively evaluate issues such as volume limits and coverage impairment due to the proximity of dose-limiting structures and demonstrate whether any single technique is superior. However, given the relatively low incidence of this pathology, it is unlikely that a prospective randomized trial with adequate power can be performed, so results from cohort studies with progressively longer follow-ups will remain relevant.

CONCLUSION

In conclusion, SRS was an effective and safe treatment for recurrent AM. The previously discussed volume limitations should be noted. The results presented here, after a long follow-up, reinforce this conclusion. Patients who present multicentric disease will probably have a worse survival rate and should be referred for alternative treatments.

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