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CLINICAL INVESTIGATION

LONG-TERM OUTCOMES OF STEREOTACTIC RADIOSURGERY FOR TREATMENT OF CAVERNOUS SINUS MENINGIOMAS

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Purpose: Patients with cavernous sinus meningiomas (CSM) have an elevated risk of surgical morbidity and mortality. Recurrence is often observed after partial resection. Stereotactic radiosurgery (SRS), either alone or combined with surgery, represents an important advance in CSM management, but long-term results are lacking.

Methods and Materials: A total of 88 CSM patients, treated from January 1991 to December 2005, were retrospectively reviewed. The mean follow-up was 86.8 months (range, 17.1–179.4 months). Among the patients, 22 were followed for more than 10 years. There was a female predominance (84.1%). The age varied from 16 to 90 years (mean, 51.6). In all, 47 patients (53.4%) received SRS alone, and 41 patients (46.6%) had undergone surgery before SRS. A dose of 14 Gy was prescribed to isodose curves from 50% to 90%. In 25 patients (28.4%), as a result of the proximity to organs at risk, the prescribed dose did not completely cover the target.

Results: After SRS, 65 (73.8%) patients presented with tumor volume reduction; 14 (15.9%) remained stable, and 9 (10.2%) had tumor progression. The progression-free survival was 92.5% at 5 years, and 82.5% at 10 years. Age, sex, maximal diameter of the treated tumor, previous surgery, and complete target coverage did not show significant associations with prognosis. Among the 88 treated patients, 17 experienced morbidity that was related to SRS, and 6 of these patients spontaneously recovered.

Conclusions: SRS is an effective and safe treatment for CSM, feasible either in the primary or the postsurgical setting. Incomplete coverage of the target did not worsen outcomes. More than 80% of the patients remained free of disease progression during long-term follow-up. © 2010 Elsevier Inc.

Cavernous sinus meningiomas, stereotactic radiosurgery.

INTRODUCTION

Cavernous sinus tumors represent 1% of all intracranial neoplasms, and 41% of them are cavernous sinus meningiomas (CSM) (1). These tumors are usually close to critical neurovascular structures, such as cranial nerves and the carotid artery, and sometimes infiltrate them (2–4). As a consequence, the rate of gross total resections is highly variable (12–82%), with a cost of significant morbidity and mortality (1, 5–14). To decrease this level of complications, approaches such as stereotactic radiosurgery (SRS), or a less radical surgical treatment followed by SRS, have been used as alternative procedures, both with good results (6, 14–19).

Some particularities must be considered for the study of SRS in the treatment of CSM. The delivered dose may be limited by the location of the target, which can impair the coverage. Morbidity varying from 1.5% to 25%, consisting mainly of cranial nerve affections, has been reported (20–22).

We present here the results obtained after prolonged follow-up in patients who underwent SRS either alone or after neurosurgery and, in some of them, with the prescribed dose not matching the tumor margin because of its proximity to critical structures. This is, to our knowledge, the longest follow-up reported so far.

METHODS AND MATERIALS

Study patients

A total of 88 consecutive CSM patients, treated from January 1991 to December 2007 at the Department of Neurosurgery, Hospital San Francisco, Madrid, Spain, were retrospectively reviewed. The term “cavernous sinus meningiomas” was used only for tumors arising primarily from the cavernous sinus. Histological confirmation was not required for those diagnosed radiographically.

Our study population exhibited a female predominance (ratio, 5.3:1). Patient age varied from 16 to 90 years (mean, 51.6), and 22 patients (25%) were older than 60 years. Of the patients, 47 patients (53.4%) received SRS alone, and 41 (46.6%) had undergone

surgery before SRS. The maximal diameter of the treated tumor was ≤ 3 cm in 37 patients (42%), 3 to 5 cm in 46 patients (52.2%), and >5 cm in 5 patients (5.8%) (Table 1). The mean volume of the tumors was 3.7 cm^3 for the SRS-alone group and 5.9 cm^3 for the postoperative SRS group.

Procedures

In all cases, SRS was carried out using a linear accelerator with 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 resonance imaging (MRI) was performed, after which the stereotactic frame was placed under local anesthesia for the planning CT phase. An image fusion program was used to delimit the target volume. Three-dimensional treatment planning was made in all cases, using different planning units (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, Milan, Italy]) during the period of the study.

Dose planning was performed to cover the enhancing tumor as conformably as possible. A mean dose of 13.95 Gy (range, 13–16 Gy), median 14 Gy, was prescribed to the 73.5% (range, 50–90%) mean isodose, median 75%. The number of collimators used varied from one to five; one was used in 26 cases, two were used in 43 cases, three in 14 cases, four in four cases, and five in one case. Besides tumor volume, the maximum doses at adjacent structures, such as the optic chiasm or optic nerves, were calculated. In situations in which the tolerance dose of 8 Gy delivered to these structures was surpassed (23) (28.4% of the patients), this limit was prioritized, and the prescribed dose did not completely cover the tumor volume. Nonetheless, the dural tail was always treated.

After SRS, all patients were subjected to 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. Follow-up MRI, with and without gadolinium enhancement, was carried out after 6 and 12 months, and yearly thereafter. MRI protocols have evolved over the period of the study, along with evolutionary implementation of MRI technology, as did radiosurgically induced change interpretation. The mean follow-up was 86.8 months (range, 24–179.4 months). All patients were followed for at least 2 years and 22 patients were followed >10 years.

Table 1. Patient characteristics

Sex	
Men	14 (15.9%)
Women	74 (84.1%)
Age (y)	
≤ 60	66 (75%)
>60	22 (25%)
Surgery before SRS*	
Yes	41 (46.6%)
No	47 (53.4%)
Target coverage	
Complete	63 (71.6%)
Incomplete	25 (28.4%)
Maximal diameter of the tumor	
≤ 3 cm	37 (42%)
>3 and ≤ 5 cm	46 (52.2%)
>5 cm	5 (5.8%)

Abbreviation: SRS = stereotactic radiosurgery.

Statistical analysis

The duration of progression-free survival (PFS) was the minimal amount of time from the procedure until the onset of clinical progression or death. All eligible cases were included in the analysis of PFS. The estimation of the cumulative proportion surviving was based on Kaplan–Meier procedures (24). To analyze factors correlating with PFS, the following parameters were assessed: age (≤ 60 years vs. >60 years), sex, maximal diameter of the treated tumor, previous surgery, and completeness of the target coverage. SPSS version 12.0 (SPSS Inc., Chicago, IL) was used to analyze the results.

RESULTS

Tumor growth control at last follow-up was obtained for all the patients treated for CSM. After SRS, 65 patients (73.8%) presented with tumor volume reduction, 14 (15.9%) remained stable, and 9 (10.2%) had tumor progression. The 5-year PFS was 92.5% and the 10-year PFS 82.5% (Fig. 1). After that period and until the end of the follow-up, no recurrences were seen among the 22 patients who were followed up for >10 years. Two patients died (1 woman and 1 man); in both cases, the deaths were related to neurological complications secondary to disease progression, after 54 and 78 months, respectively.

Univariate analysis of prognostic factors was performed for PFS. Age, sex, maximal diameter of the treated tumor, previous surgery (Fig. 2), and completeness of target coverage (Fig. 3) did not show a significant association with PFS. Because of the low number of deaths, no overall survival study was done. Among the patients who experienced progression, 5 underwent neurosurgery, 1 patient underwent another SRS treatment, and 1 patient received external beam radiotherapy. The other 2 patients were kept under surveillance and did not undergo any other treatment until the end of their follow-up.

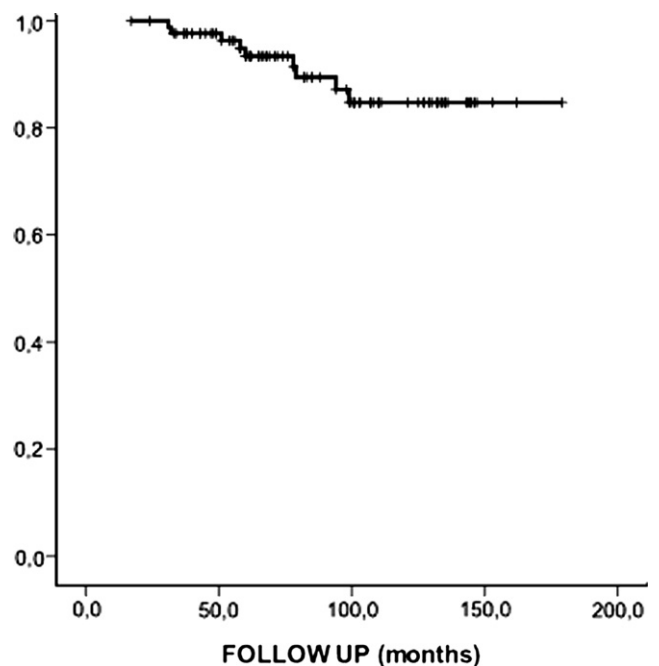


Fig. 1. Progression-free survival (PFS) of patients with cavernous sinus meningiomas (CSM).

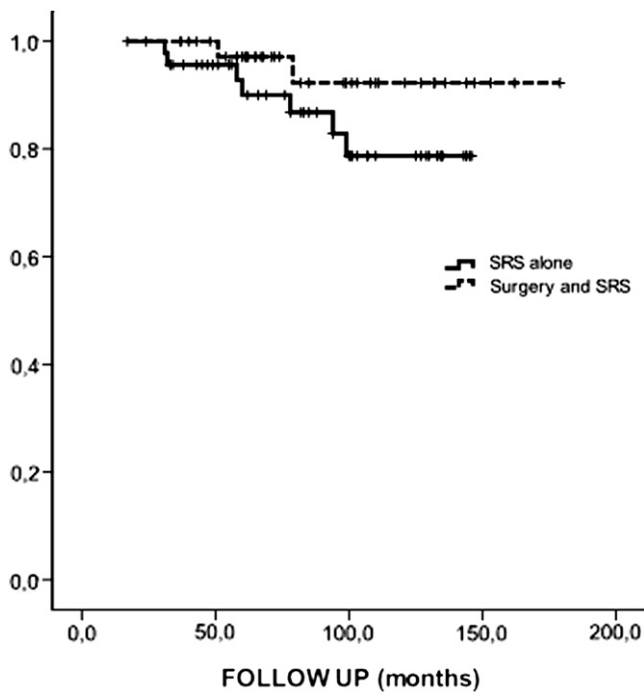


Fig. 2. Progression-free survival (PFS) of patients who underwent stereotactic radiosurgery (SRS) alone compared with patients who underwent surgery and SRS.

Among the 88 treated patients, 45 patients (51.1%) presented with clinical improvement of symptomatology related to cranial nerves, 26 (29.5%) remained stable, and 17 (19.3%) developed new or worsening cranial nerve deficits

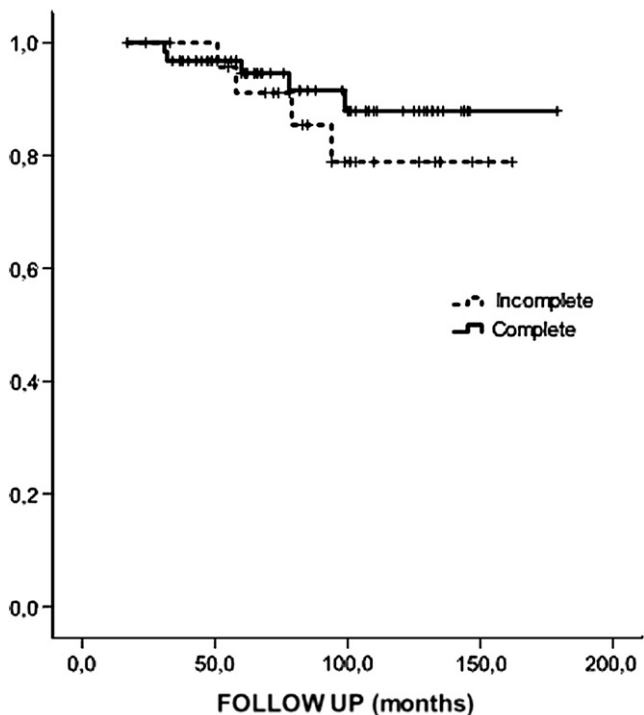


Fig. 3. Progression-free survival (PFS) of patients who had complete coverage of the target on the stereotactic radiosurgery (SRS) procedure compared with patients who did not have complete target coverage.

as a result of the SRS. In 3 patients, the morbidity was related to the optic nerve, in 2 patients, to the oculomotor; and in 1 patient, to the abducent. Nine patients presented trigeminal hypoesthesia, and three impairment of the VI pair (1 patient also had a trigeminal deficit). Six spontaneous recoveries were observed, all in patients who had trigeminal symptomatology. No severe morbidity resulting from SRS or any injuries to large cranial arteries were noted among this group of patients.

DISCUSSION

These data show that SRS as associated with good outcomes in the treatment of CSM patients, after a noticeably long follow-up, even when full coverage of the target was not possible. We observed a tendency toward stabilization of local control at a plateau, as no more recurrences were detected after 8.25 years of follow-up.

Historically, CSMs were treated surgically; however this surgery, aiming to completely remove the tumor, necessarily involves opening the sinus so that the tumor mass can be dissected away from the intracavernous cranial nerves and from the carotid artery. Published data by Jesus *et al.* indicate a considerable risk of recurrence (20% in 5 years), even after radiologic confirmation of complete resection at a cost of severe morbidity (7). Other series, also after complete resection, report similar outcomes, with recurrence rates ranging from 9.6% to 25% (8, 9, 11).

This recurrence level may be explained by microscopic characteristics of the meningioma cells. Infiltration into cranial nerves has been documented by Larson *et al.* According to them, complete resection is not feasible without the resection of the involved cranial nerve (2). Kotapka *et al.* have reported levels as high as 42% of carotid artery involvement, verified by pathological revision of surgical specimens (4). In fact, these tumor cells have a patent tendency to infiltration, and it seems to occur along the connective tissue plans down with the cavernous sinus, a characteristic that is heightened by the odd structure of this anatomic site (3). That is probably the reason why some resections seemed complete but, in fact, were not.

Also, the high rate of procedure-related morbidity renders alternative options more attractive. Partial resection in combination with SRS is a valid strategy because a less radical approach may result in less morbidity, with comparable local control. Another possibility is isolated SRS, for smaller tumors, when decompression is not necessary. In recent years, many detailed results on this topic have been published (Table 2) (14–19, 22, 25–34).

Most of the cited studies refer to the acquired experience with the use of a Gamma Knife. The majority of the articles about the experience with linear accelerators have included other cavernous sinus lesions besides meningiomas, and this hampers comparison among series. Our patients showed 92.5% 5-year PFS and 82.5% 10-year PFS, with a considerable number of patients reaching and surpassing this follow-up period. These results corroborate and also strengthen previous

Table 2. Series of patients with cavernous sinus meningiomas who underwent radiosurgery

Year	First author	Patients (n)	Mean f/u (mo)	Prior surgery	SRS alone	PFS 5 y	PFS 10 y	New CN deficits	GK / Linac
1999	Morita	88	35	49	39	95%	—	10.2%	GK
1999	Liscak	67	19	24	43	—	—	3.8%	GK
2000	Roche	80	30.5	30	50	92.8%	—	5.8%	GK
2001	Shin	40	42	28	12	—	82.3%	20%	GK
2002	Spiegelman	42	36	9	31	97.5%	—	7.5%	Linac
2002	Nicolato	156	48.9	81	75	96.5%	—	1%	GK
2002	Lee	159	35	76	83	93.1%	93.1%	9%	GK
2003	Iwai	42	49.4	22	20	92%	—	4.8%	GK
2004	Maruyama	40	46	23	17	94.1%	—	25%	GK
2004	Kuo	57	42	—	—	97%	—	2.2%	GK
2005	Metellus	36	63.6	13	23	94.4%	—	0%	GK
2005	Pollock	49	58	0	49	80–85%	—	10%	GK
2007	Hasegawa	115	62	66	49	87%	73.0%	12%	GK
2009	Kimball	49	50	12	38	100%	98%	3.5%	Linac
2010	Spiegelman	102	67	33	69	98%	—	4%	Linac
2010	This study	88	86.8	41	47	92.5%	82.5%	12.5%	Linac

Abbreviations: CN = cranial nerves; f/u = follow-up; GK = Gamma Knife; PFS = progression-free survival; SRS = stereotactic radiosurgery.

conclusions about the efficacy of this strategy, although there has been constant doubt about the outcomes on the long run (12, 17–19, 26, 28, 29, 32–39). Kallio *et al.*, studying 935 meningioma patients, observed a median postoperative time until recurrence of 7.5 years (40). Since the Simpson study, it has been known that a long follow-up for patients with CSM, typically slow-growing tumors, is essential, as recurrences manifest after an average period of 5 years, and long-delayed recurrences are clearly possible (41).

Two of the presented studies, by Lee *et al.* and Kimball *et al.*, reported remarkably better results of local control over 10 years. However, both of them had notably lower median follow-up. Lee *et al.* report having maintained results between 5 and 10 years, which may be a consequence of a low number of patients whose follow-up reached this interval (30). In addition, Kimball *et al.* reported that some patients were lost to follow-up, which could be another explanation for the disparity. Longer follow-up of such series are needed to make comparisons acceptable (19).

Regarding morbidity, SRS targeting cavernous sinus usually causes delayed cranial neuropathies (30). As reported in Table 2, their incidence after SRS can be highly variable, ranging from 0% to 25% of cases. This fact places our rates among those previously published, corroborating prior conclusions that the procedure is sufficiently safe (15–19, 22, 26–34, 42).

The Target

Conformity is a fundamental principle of SRS. Given the proximity of CSM to radiosensitive structures, such as the optic nerve, chiasm, and brainstem, dilemmas may emerge when this proximity prevents full-dose radiation from being delivered to the tumor. In such situations, either the dose may be reduced, risking compromising tumor control, or part of the tumor may be undertreated (43).

The importance of the dural origin of meningiomas is well established in surgical practice, as reflected by Simpson's grades, but may be equally significant in radiosurgical practice (43). DiBiase *et al.* treated, with Gamma Knife radiosurgery,

137 meningioma patients, among whom 29 had CSM. These investigators report better results when the dural tail was included in the target (44). Meanwhile, Rogers *et al.* point out that this finding may, in fact, be related to the tumor volume instead of the inclusion of the tail itself in the treatment target, as the dural tail extension often increases the size and the complexity of a SRS plan. Also, the tumor volume was, as mentioned above, the only significant variable related to local control, on multivariate analysis. Moreover, the authors provide some evidence to reinforce their conclusions: The dural tail is almost entirely hypervascular; meningioma clusters are only occasionally observed at this site; this is not considered a criterion for resection extent; and there is no evidence that recurrences are more likely to occur in the dural tail (45).

We suggest another interpretation for this fact: it is known that at least part of the effect of the SRS comes from vascular occlusions after intima hyperplasia (46). Treating the dural origin may compromise the vascular supply of the tumor, leading to its devascularization. This possibility is reinforced by the fact that 75% of the recurrences involve the dura outside the treatment field (43). The histopathological investigation by Szeifert *et al.* on specimens obtained from craniotomies in patients who had undergone SRS support this finding. Microvascular endothelial cells are the primary targets of single high-dose radiation (47).

Shin *et al.*, on the other hand, report worse results when complete coverage of the target could not be achieved. This discrepancy may be explained by the fact that the dural tail could not necessarily be inside the target. Because there is no precise description, it may be inferred that the gap in the prescribed volume would be acceptable whenever there is a risk of compromising optical nerves and chiasm. Another unknown variable is the number of malignant tumors, to which this strategy may be inadequate. In addition, as the size of the tumor was one of the reasons not to treat part of its volume, this group of patients could simply harbor larger tumors, which could explain the worse results (29).

This study has the evident limitations of a single-institution, retrospective series of cases; and despite the rarity of the disease, it had a small number of patients, which can impair the reliability of the conclusions, for example, about the results with partial coverage of the radiosurgical target. No differences in PFS were demonstrated, according to potential prognostic factors, probably because of a small sample size. 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 on cohort studies, with progressively larger follow-up, will maintain their relevance.

CONCLUSION

In conclusion, based on our study findings, SRS is a safe treatment for CSM, with acceptable levels of local control and with reasonable levels of long-term toxicity despite its proximity to important structures. The results presented here, after a long follow-up, reinforce this conclusion. Covering the entire tumor remains the ideal strategy in achieving long-term tumor control, although, in practice, this may not always be feasible. In that situation, we advocate that the dural tail be treated with the adequate dose, instead of risking higher levels of complications due to possible lesions of sensitive structures that lie near the target.

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