Treatment of Cavernous Sinus Tumors with Linear Accelerator Radiosurgery

ABSTRACT—Since 1989, 79 patients with benign or malignant cavernous sinus tumors, have been treated at Stanford University with linear accelerator (linac) radiosurgery. Radiosurgery has been used as (1) a planned second-stage procedure for residual tumor following surgery, (2) primary treatment for patients whose medical conditions preclude surgery, (3) palliation of malignant lesions, and (4) definitive treatment for small, well-localized, poorly accessible tumors. Mean patient age was 52 years (range, 18 to 88); there were 28 males and 51 females. Sixty-one patients had benign tumors; 18 had malignant tumors. Mean tumor volume was 6.8 cm³ (range 0.5 to 22.5 cm³) covered with an average of 2.3 isocenter (range, 1 to 5). Radiation dose averaged 17.1 Gy. Mean follow-up was 46 months. Tumor control or shrinkage, or both, varied with pathology. Radiographic tumor improvement was most pronounced in malignant lesions, with greater than 85% showing reduction in tumor size; benign tumors (meningiomas and schwannomas) had a 63% control rate and 37% shrinkage rate, with none enlarging. We concluded that stereotactic radiosurgery is a valuable tool in managing cavernous sinus tumors. There was excellent control and stabilization of benign tumors and palliation of malignant lesions.

Stereotactic radiosurgery is playing an increasing role in the treatment of many small to medium-sized cavernous sinus tumors, particularly those that occur in patients who are poor surgical candidates.¹⁻¹⁰ Among this patient population, treatment is being used for both primary and residual tumors following conventional surgery or fractionated regional radiation therapy.^{5,7,8,11} The primary goal of radiosurgical treatment is tumor control and shrinkage for benign tumors and palliation for malignant lesions. Since 1989, 79 patients with cavernous sinus tumors (both benign and malignant) have been treated at Stanford University Medical Center with

linac radiosurgery. This group of patients was studied retrospectively.

METHODS

The mean age of the patients was 52 years (range, 18 to 88). There were 28 males and 51 females. Fifty-four of the 79 patients (68%) were clinically symptomatic at the time of treatment; 25 patients (32%) were asymptomatic but treated after serial magnetic resonance imaging (MRI) showed tumor progression. Forty-

Table 1. Types of Cavernous Sinus Tumors

Benign tumors	61
Meningiomas	44
Schwannomas	8
Pituitary adenomas (lateral)	7
Craniopharyngioma	2
Malignant tumors	18
Metastatic	12
Nasopharyngeal carcinoma	6

eight patients (61%) had undergone previous open surgery for tumor resection; 11 (14%) had surgical biopsy to confirm diagnosis. Twenty patients (25%) had a presumptive diagnosis made on radiographic appearance because of classic lesion appearance on MRI (e.g., cavernous sinus meningiomas), proximity to primary lesions site (e.g., lateral pituitary tumors or nasopharyngeal carcinomas), or primary malignant disease (widely metastatic cancer). The various tumor types are shown in Table 1. Fourteen patients (18%) had previous fractionated cranial radiotherapy with a mean dose of 51 Gy (range, 41 to 56 Gy).

The mean tumor volume treated with stereotactic radiosurgery was 6.8 cm³ (range, 0.5 to 22.5 cm³), covered with an average of 2.3 isocenters (range, 1 to 5). Mean radiation dose to tumor margin was 17.1 Gy (range, 12 to 21 Gy). Based on tumor location, presenting symptoms involved primarily cranial nerve deficits; other presenting symptoms are shown in Table 2.

Patients were treated with linac stereotactic radiosurgery using a technique initially described by Winston and Lutz¹² and later described by Adler et al.¹³ Localization was performed with either computed tomography (CT) or MRI using 3-mm slices. Multiple noncoplanar arc radiation from either a 4- or a 6-mV linac was used, with an 80- to 100-cm source to axis distance. Circular secondary collimators ranged in diameter from 7.5 mm to 35 mm (mean, 14.3 mm). Treatment dose was selected on the basis of tumor size, number of isocenters, any previous history of conventional radiotherapy, and a desire to treat these small to moderate sized tumors to approximately 15 to 20 Gy whenever possible while limiting the dose to the optic nerve and chiasm to less

than 8 Gy. Lower tumor doses were prescribed when necessary to limit radiation to the optic apparatus or when treating larger tumor in the series (>15 cm³). Treatment dose varied between 12 and 21 Gy, which was prescribed to the 80% isodose contour at the edge of contrast-enhancing tumor.

Clinical follow-up was obtained at 3, 6, and 12 months after radiosurgery and then annually. Neurological status was recorded with special emphasis on cranial nerve function, and any acute and long-term complications were noted. Radiographic follow-up in the form of MRI as obtained at 6 and 12 months and annually thereafter for benign tumors and at 3 and 6 months and then every 6 months or when clinically indicated for malignant tumors. These studies were used to evaluate treated tumors for size and evidence of necrosis, as well as any surrounding brain edema or necrosis. Mean clinical and radiographic follow-up averaged 46 months (range, 12 to 73).

RESULTS

Radiographic Response

Tumor response following stereotactic radiosurgery varied with pathology. Of the 61 patients with benign lesions, tumor control (stabilization) following radiosurgery was noted in 39 (63%) and tumor shrinkage was noted in 22 (37%) (Fig. 1). Eleven of the 44 meningiomas (25%), four of the eight schwannomas (50%), and three of the seven pituitary tumors (43%) showed evidence of loss of central contrast enhancement (possible tumor necrosis) on MRI 1 to 3 years after radiosurgery. None of the benign tumors > 12 cm³ decreased in size during the period of review, however, all of these larger tumors were stabilized on follow-up images. Malignant tumors generally showed pronounced radiographic response to stereotactic radiosurgery with 15 of 18 tumors (83%) showing decrease in tumor size (Fig. 2) and 1 of 18 (6%) showing tumor stabilization over a 16-month mean follow-up. Only 2 of 18 patients (11%) had tumor increase over this same interval.

Table 2. Clinical Symptoms*

	Initial Presentation	Changes in Symptoms after Linac Radiosurgery	
		Improvement	Resolution
Cranial nerve deficits	45	4	32
Headache	11	6	3
Nausea/vomiting	7	7	
Proptosis/exophthalmos	7	3	
Seizures	4		
Asymptomatic but with increase in tumor size on MRI	25		

*Some patients presented with more than one clinical symptoms, including multiple cranial nerve deficits.

Figure 1. A 78-year-old woman presented with diplopia and proptosis. (A) Evaluation showed a right cavernous sinus meningioma seen on pretreatment gadolinium enhanced axial MRI. (B) One year after treatment with a 20-Gy stereotactic radiosurgical dose, the tumor was smaller in size, shown on gadolinium-enhanced axial MRI. The patient's diplopia resolved and proptosis improved.

Clinical Response

For patients with benign tumors, neurological status was improved in 26 of 61 patients (43%) and unchanged in 31 of 61 patients (51%). Four of 61 patients

(7%) with benign tumors were clinically worse on follow-up exam as a result of radiation injury. All subsequently improved with steroid therapy. Of the 18 patients with malignant lesions, 7 (39%) improved, 7 (39%) had stable neurological exams, and 4 (22%) were

Figure 2. A 68-year-old man presented with a third nerve palsy and headaches. Evaluation revealed a left cavernous sinus squamous cell carcinoma. The patient was treated with a 12-Gy dose of stereotactic radiosurgery. Compared with pretreatment gadolinium-enhanced coronal MRI (A), the tumor was smaller in size 3 months later (B). Clinically, the third nerve palsy resolved.

Table 3. Complication from Radiosurgery

Cranial nerve deficits		
Transient		10
trigeminal nerve	6	
diplopia	3	
trigeminal and facial nerve	1	
Permanent		2
facial nerve	1	
vagus and hypoglossal nerve	1	
Symptomatic radiation injury		2
Asymptomatic radiation injury		2
Immediate		7
Nausea/vomiting	5	
Significant pin site pain requiring intravenous analgesics	2	

clinically worse during the follow-up interval (mean follow-up was 16 months). Improvement or resolution of specific clinical symptoms is shown in Table 2. Seven of the 18 patients (39%) with malignant tumors died from systemic disease progression during the follow-up period.

Complications

Acute symptoms were minor and primarily consisted of nausea and vomiting in 5 patients (6%). These patients were treated early in our series; this complication was minimized by administering prophylactic dexamethasone and promethazine hydrochloride to patients treated later in the series. Delayed complications included cranial nerve injury or radiographic and clinical evidence of radiation necrosis (Table 3). Ten patients (13%) developed transient new cranial nerve deficits consisting of trigeminal hypesthesia (8 patients) and diplopia (2 patients). In all of these patients, symptoms developed between 6 and 16 months after radiosurgery but resolved completely within 12 months. There were 2 cases of brain necrosis, 1 of which resulted in trigeminal nerve paresthesias, and 3 cases of asymptomatic radiation edema, none of which resulted in permanent deficits.

CONCLUSIONS

The morbidity and mortality of surgical removal of cavernous sinus tumors remain appreciable, despite advances in microsurgical techniques and instruments. Recent reports document a 6% mortality rate, a 30% morbidity rate, and only a 60 to 70% gross total tumor excision rate for patients with cavernous sinus tumors.^{14,15} Stereotactic radiosurgery is a conceptually attractive technique for managing many benign cavernous sinus tumors, with the goal of preserving or improving

neurological function while preventing tumor growth. Previous larger series of skull base meningiomas (many of which were in the cavernous sinus) treated with radiosurgery showed control or regression rates of greater than 90%.^{5,7,10} In a smaller gamma knife series that focused exclusively on cavernous sinus meningiomas, there was a 100% tumor control rate during 26 months of follow-up.¹⁶ A series of 13 patients with pituitary adenomas involving the cavernous sinus underwent stereotactic radiosurgery to residual cavernous sinus tumor after transsphenoidal surgery.¹⁷ All patients showed decrease in tumor size on follow-up MRI, and 12 of 13 had normalization of hormonal levels. Although early results in these series are encouraging, long-term (10 to 15-year) follow-up is lacking.

For patients with malignant cavernous sinus tumors, stereotactic radiosurgery serves a largely palliative role.¹⁸ Patients with widespread metastatic disease have limited prognosis and may represent higher surgical risk because of poor medical condition. In these cases, the noninvasiveness of stereotactic radiosurgery is attractive. For patients with multiple metastases, both the cavernous sinus tumor and the other sites can be treated at a single radiosurgical sitting.

Radiographic Response to Size

Most tumors in this series were less than 10 cm³. These small lesions represent ideal radiosurgical targets because complication rates are proportionally lower.¹⁹ Many centers, including ours, use slightly smaller doses for larger tumors (greater than 10 to 15 cm³), with the possible trade off being decreased tumor kill. Although all benign tumors larger than 12 cm³ stabilized without evidence of growth, no tumor of this size decreased during follow-up. This implies that when mass effect is an issue, larger cavernous sinus tumors, especially benign meningiomas or schwannomas, should be at least subtotally resected. Residual tumors can be safely treated with radiosurgery after surgical debulking.

Tolerance of Cranial Nerves

Given the location of most skull base meningiomas, cranial nerves must necessarily be treated to full dose. The observed radiation tolerance of cranial nerves in this series confirms other reports that have noted the radiation resistance of most motor cranial nerves.^{5,8,11} Ten patients in this series developed cranial neuropathies (13%), 8 with ipsilateral trigeminal nerve dysfunction (primarily brief periods of facial pain) and 2 with diplopia, but none suffered permanent injury because all resolved over a period of 12 months. Other authors have described a similar low incidence of cranial

neuropathies after stereotactic radiosurgery in and around the cavernous sinus.⁵

Limitations of the Study

As with other reported series of radiosurgery for cavernous sinus tumors, the primary shortcoming of this study is the relatively short follow-up, particularly with benign tumors. Since cavernous sinus meningiomas and schwannomas may exist for years without appreciable change in size, longer follow-up is needed before results can be deemed permanent. A second limitation is the heterogeneity of tumor types, because many different benign and malignant lesions can involve the cavernous sinus. Ideally, a series of larger study populations, each focusing on a specific type of tumor, might provide more conclusive results. Finally, there is appreciable patient heterogeneity in our population. Fourteen patients had previous fractionated radiotherapy, and 48 had previous surgical resections.

Conclusion

Patients with small (<10- to 15-cm³) cavernous sinus tumors without significant mass effect represent ideal candidates for radiosurgery. Additionally, in debilitated patients who are not candidates for conventional surgery or in patients requiring palliation of malignant lesions, radiosurgery remains a good option. However, patients with larger lesions or tumors causing acute neurological deterioration (i.e. visual loss) are best treated with microsurgical debulking, reserving radiosurgery for treatment of any residual tumor. Our experience to date suggests that 16 to 20 Gy in a single fraction is both safe and effective for most cavernous sinus tumors.

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COMMENTS FOR PUBLICATION

The review of Chang et al describing the Stanford University experience with 79 cavernous sinus tumors contributes additional important information on linac radiosurgery treatment of the cavernous sinus. Thorough discussion of the treatment technique (although used for a variety of tumor types) is a strong point of the paper. It is noteworthy that a proportion of treatment planning was done using CT scanning alone with 3-mm slices. Response of both benign and malignant tumors is noted along with a complete description of complications. Late cranial nerve injury occurred in 13% of patients, although all deficits resolved with steroid therapy. The authors also report 100% control in 61 benign tumors and 89% in malignant tumors followed for 15 months. However, 22% of these malignant tumors had worsening neurological function, at least temporarily.

The authors' recommended dose of 16.0 to 20.0 Gy is a conclusion based on their experience. Our local control with several benign tumors such as meningiomas has been 100% with mean dose significantly

lower (13.1 Gy). In addition, virtually all treatment planning is done with 1-mm slices with CT fused to 1.5-mm slice MRI. The authors note 3-mm slice thickness and treatment planning with CT alone. Improved resolution allows improved dose conformality because target configuration is more clear. Both dose and conformality may contribute to complication risk. Our complications have also been fewer. Certainly one will wonder if some local control will be sacrificed, but this

has not been our experience to date. Chang et al have also maintained excellent local control with malignant tumors where higher doses may be more important. The paper adds to our knowledge regarding treatment of the cavernous sinus with radiosurgery. We agree that it is conceptually attractive and have had similar excellent results to date.

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