VISUAL FIELD PRESERVATION AFTER MULTISESSION CYBERKNIFE RADIOSURGERY FOR PERIOPTIC LESIONS

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OBJECTIVE: The restricted radiation tolerance of the anterior visual pathways represents a unique challenge for ablating adjacent lesions with single-session radiosurgery. Although preliminary studies have recently demonstrated that multisession radiosurgery for selected perioptic tumors is both safe and effective, the number of patients in these clinical series was modest and the length of follow-up limited. The current retrospective study is intended to help address these shortcomings.

METHODS: Forty-nine consecutive patients with meningioma (n = 27), pituitary adenoma (n = 19), craniopharyngioma (n = 2), or mixed germ cell tumor (n = 1) situated within 2 mm of a "short segment" of the optic apparatus underwent multisession image-guided radiosurgery at Stanford University Medical Center. Thirty-nine of these patients had previous subtotal surgical resection, and six had previously been treated with conventional fractionated radiotherapy (6). CyberKnife radiosurgery was delivered in two to five sessions to an average tumor volume of 7.7 cm^3 and a cumulative average marginal dose of 20.3 Gy. Formal visual testing and clinical examinations were performed before treatment and at follow-up intervals beginning at 6 months.

RESULTS: After a mean visual field follow-up of 49 months (range, 6–96 mo), vision was unchanged postradiosurgery in 38 patients, improved in eight (16%), and worse in three (6%). In each instance, visual deterioration was accompanied by tumor progression that ultimately resulted in patient death. However, one of these patients, who had a multiply recurrent adrenocorticotropic hormone-secreting pituitary adenoma, initially experienced early visual loss without significant tumor progression after both a previous course of radiotherapy and three separate sessions of radiosurgery. After a mean magnetic resonance imaging follow-up period of 46 months, tumor volume was stable or smaller in all other cases. Two patients died of unrelated nonbrain causes.

CONCLUSION: Multisession radiosurgery resulted in high rates of tumor control and preservation of visual function in this group of perioptic tumors. Ninety-four percent of patients retained or improved preradiosurgical vision. This intermediate-term experience reinforces the findings from earlier studies that suggested that multisession radiosurgery can be a safe and effective alternative to either surgery or fractionated radiotherapy for selected lesions immediately adjacent to short segments of the optic apparatus.

KEY WORDS: CyberKnife, Meningioma, Pituitary adenoma, Stereotactic radiosurgery

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Single-session radiosurgical ablation has become a generally accepted technique for managing a spectrum of small cranial base and inaccessible brain lesions (3, 14, 19, 21, 22, 28, 30, 33, 37, 45, 48, 51–53, 55–57, 62–65, 68, 70, 71, 74, 75). Nevertheless, the proximity of the anterior visual pathways (optic nerve and optic chiasm) poses a particular challenge for ablating "perioptic" tumors; it is widely acknowledged that the unique radiation sensitivity of the normal optic apparatus precludes conventional radiosurgery when a lesion is within 2 mm of the anterior visual pathways (23, 25, 35, 36,

42, 49, 54, 66, 71). In lieu of primary radiosurgery, the most widely used strategies for managing tumors that abut the optic chiasm and nerve involve either standard fractionated radiotherapy or a combination of microsurgical resection followed by radiosurgical ablation.

Tumors involving the anterior visual pathways are frequently managed with conventionally fractionated focal radiation therapy, during the course of which, a lesion and the immediately surrounding normal brain is bathed with tumoral-static doses of radiation. Extensive clinical experience has established dose and fractionation regimens for radiotherapy that are quite effective for a range of neoplasms and result in approximately a 3% risk of optic neuropathy for pituitary tumors (7, 20, 27, 41, 46, 50) and less than 3% for cranial base meningiomas (38, 39, 44, 58, 61, 73). However, tumor control and, especially, tumor shrinkage after radiotherapy for many perioptic lesions may not be quite as good as radiosurgery (15, 18, 43). Furthermore, because of spatial inaccuracies in patient set-up, standard radiation therapy methods, when compared with stereotactic radiosurgery techniques, irradiate a larger region of normal brain, which can include a longer length of optic apparatus as well as significant portions of the pituitary, hypothalamus, and medial temporal lobe. Although the short-term side effects of such irradiation seem minor, the longer-term consequences are largely unstudied and potentially deleterious. Consistent with such conjecture, pituitary failure occurring a decade or more after regional radiation therapy is a well-described phenomenon (2, 16). The risk of hypopituitarism with conventional radiotherapy is reported to be 30 to 70% (40, 47, 72, 76). Second malignancies and temporal lobe necrosis are other established late complications (6, 8, 26, 34, 59, 72).

In selected perioptic lesions, a preliminary, open microsurgical resection that removes tumor compressing or immediately juxtaposed to the optic apparatus can enable later radiosurgical ablation. Although this approach is frequently possible, open surgery is inherently associated with additional case-specific risks, not least of which is the very real potential for visual loss accompanying the manipulation of often compromised anterior visual pathways.

The dose gradient that can be achieved with all forms of single-session photon radiosurgery is typically inadequate for the safe treatment of perioptic lesions. Furthermore, in many cases, it is impossible to reliably delineate an optic apparatus that is significantly effaced or displaced by tumor, even with the best of computerized imaging. When any type of radiation is being considered in such patients, one must find a way to mitigate for the very real possibility that portions of the radiation sensitive anterior visual pathways may lie within the region of marginal prescribed dose; in fact, prudence dictates that one must assume this to be true. With the goal of protecting adjacent brain structures, such as the optic chiasm, the recent emergence of image-guided radiosurgery now enables the principles of limited multisession treatments to be used in selected clinical circumstances as an alternative to surgical resection and conventionally fractionated radiation therapy (XRT). Radiosurgical dose homogeneity also assumes special importance, specifically in those situations in which the optic apparatus cannot be visualized; again, one must assume that the nerve is getting the maximal dose. Fortunately, the nonisocentric beam delivery and inverse planning algorithms that are used in image-guided radiosurgery (as opposed to isocentric multishot technology) enable a significant measure of dose homogeneity.

On the basis of this rationale, multisession radiosurgery was used to manage selected perioptic lesions at Stanford University Medical Center starting in 1997 (42, 54). Although previous publications described our preliminary experience with this technique, the size of these series was modest, and the average follow-up period was only 29 months (54). These limitations precluded more definitive conclusions about the longer-term efficacy and safety of multisession radiosurgery for tumors adjacent to the visual pathways. In the present study, we extend the length of follow-up of our previous publications and extrapolate these observations to a small number of other lesions in and around the optic apparatus such as craniopharyngioma.

PATIENTS AND METHODS

Patient Population

Clinical information obtained from patients undergoing CyberKnife radiosurgery at Stanford University Medical Center is maintained in an institutional review board-approved prospective database. Within this database, there were 49 consecutive "perioptic" tumors located within 2 mm of a "short segment" of the optic apparatus as determined by magnetic resonance imaging (MRI) scans and which were all greater than 3 years postradiosurgery treatment. The definition of the term "short segment" became gradually more expansive over the duration of this study as we acquired experience and confidence in the relative safety of multisession radiosurgery. The earliest treated lesions were smaller and tended to just "touch" the nerves or chiasm. In the later stages of this experience, the length of the immediately adjacent anterior visual pathway was "estimated" to be generally less than 2 cm, although it is important to note that this structure could not in many cases be confidently visualized (and, therefore, measured) even with the best of MRI scans, especially when the nerve was displaced by tumor. In approximately 50% of the cases, the lesion obscured or displaced the optic apparatus. Once characterized as a "perioptic" tumor, multisession radiosurgery was offered to all the patients in this series.

Of the 49 patients, there were 26 (53%) women and 23 (47%) men with a mean age of 49 years (range, 17–86 yr). Six (12%) patients had a history of previous standard radiotherapy. Thirty-nine (80%) patients had previously undergone at least one open surgical resection (craniotomy or transphenoidal resection), for a total of 53 operations. Before undergoing radiosurgery, 35 out of 49 (71%) patients experienced a range of visual field deficits as documented by formal ophthalmo-

TABLE 1. Characteristics of 49 patients in this series[a]

Sex, no. (%)	
Male	26 (53)
Female	23 (47)
Age (yr)	
Mean	49
Range	17–86
Previous radiotherapy, no. (%)	6 (12)
Previous surgery, no. (%)	39 (80)
Visual field deficits, no. (%)	35 (71)
Tumor type	
Meningioma	27
Pituitary adenoma	19
Craniopharyngioma	2
Mixed germ cell tumor	1
Mean target volume (cm^3)	7.7 (range,1.2–42)
Mean marginal dose (Gy)	20.3 (range, 15–30)
Mean maximal dose (Gy)	25.5 (range, 18–43)
Number of treatment sessions, no. of patients (%)	
5	19 (39)
4	2 (4)
3	17 (35)
2	11 (22)
Mean conformality index *(PIV/TIV)*	1.40 (range, 1.01–1.88)
Mean modified conformality index $(TIV \times PIV)/TV^2$	1.20 (range, 0.66–1.67)

[a] PIV, prescribed isodose volume; TIV, tumor in isodose volume; TV, tumor volume.

logic testing. *Table 1* summarizes patient characteristics for this series.

Pathological and Detailed Anatomic Characteristics

The lesions treated in this series were classified with reference to both histopathology and the immediate adjacent cranial base location. For the 10 nonoperated patients with meningioma, a presumptive diagnosis was established based on MRI characteristics, particularly the pattern of contrast enhancement. Although many of the 27 meningiomas straddled more than one anatomic location, the primary tumor site was judged to be either the medial sphenoid wing (n = 3), cavernous sinus alone (n = 9), cavernous sinus with posterior orbital involvement (n = 6), orbital apex (n = 2), petroclival (n = 1), or tuberculum sella (n = 6). By definition, every tumor was within 2 mm of, and sometimes even displacing or completely obscuring, portions of the anterior visual pathways. In the latter situation, it was not possible to delineate the boundaries of the optic apparatus, even on high-quality, thin-section MRI scans.

There were 19 cases of histologically confirmed residual and recurrent pituitary adenoma. These lesions were hormonally active in seven patients (acromegaly, n = 4; Cushing's disease, n = 2; prolactinoma, n = 1), but nonsecreting in the remaining 12 cases. On contrast computerized imaging, these pituitary tumors involved variable portions of the sella and adjacent cavernous sinus and had a suprasellar portion that was situated within 2 mm of, immediately adjacent to, or displacing the anterior visual pathways. The two craniopharyngioma in this study, one residual and one recurrent, consisted of solid tumor intimately affixed to the posterior chiasm. Finally, in the single instance of mixed germ cell tumor, the residual lesion was located in the floor of the anterior third ventricle.

Clinical Assessment

Each patient in this study was evaluated before radiosurgery by clinical examination and thin-slice contrast-enhanced MRI or contrast high-resolution computed tomographic (CT) scans and underwent formal visual field testing. Serum hormone levels were measured when appropriate in patients with hormonally active pituitary adenoma. A multidisciplinary team of neurosurgeons, radiation oncologists, and, in many cases, a neuroradiologist determined treatment eligibility. Informed consent was obtained from all patients before enrollment in this institutional review board-approved clinical study.

Radiosurgical Technique

For radiosurgical planning, thin-slice, high-resolution CT images were obtained (after the intravenous administration of 125 ml of Omnipaque contrast [iohexol, 350 mgI/ml; Nycomed, Inc., Princeton, NJ]), using either a GE Light Speed 8i or 16i Scanner (Milwaukee, WI). After network transfer to the CyberKnife (Accuray, Inc., Sunnyvale, CA) treatment planning workstation, the treating surgeon manually outlined on axial images the target volumes and critical structures; there was simultaneous overlay of these contours on coronal and sagittal reconstructions. With experience, we found that the entire noneffaced anterior visual pathway, including both optic nerves and chiasm, could be readily delineated on thin-section (multidetector) CT scans, in conjunction with reconstructed images through the cranial base. When this could not

be performed, an MRI-CT fusion was performed (31 out of 49 patients) using thin-section MRI scans and the commercially available software provided with the CyberKnife. Not infrequently, portions of the anterior visual pathways were displaced or obscured by tumor and, therefore, could not be confidently visualized with any imaging study.

Although a small number of treatment plans were designed in this series using forward planning algorithms, for the vast majority, a previously described inverse planning method was used. This optimization technique seeks to find a maximally conformal solution that simultaneously respects the dose constraints specified for certain critical structures such as the optic chiasm and nerve (1). After iteratively computing a series of conformal radiosurgical treatment volumes, dose-volume histograms for both the target region and critical structures were used to evaluate and select the optimal treatment plan.

Because, by definition, the optic chiasm and proximate optic nerves abutted the tumor in most patients, it was not possible to administer a significantly lower dose to the contiguous portions of these structures than that administered to the margins of the target volume. Nevertheless, the standard inverse treatment planning technique of the CyberKnife was used to design plans that attempted to lower dose within radiographically visible portions of the visual pathways as well as those regions where this structure was thought to be, even though it was invisible on imaging studies.

Dose Selection

The attending neurosurgeon and radiation oncologist jointly determined the marginal and maximal dose, as well as the number of sessions. This decision was influenced by a multitude of factors including tumor volume, proximity and extent of irradiated optic nerve, as well as a previous history of radiation therapy. Although biological equivalent dose formulas were used at first (*Table 2*), it is worth emphasizing that the initial choice of number of sessions in this study was, in large measure, empirically based, having been derived from an earlier experience with multisession frame-based radiosurgery in patients with no other treatment options (three fractions administered over 30 h). Although, as a general rule, every effort was made not to exceed a maximum of 8 Gy per session to any portion of the anterior visual pathway, when this structure was displaced and could not be delineated separately from tumor, it was generally impossible to meet this objective. The maximal number of sessions used (five sessions) was reserved for patients (19 out of 49 patients) with the longest involvement of the optic apparatus and where the nerve or chiasm was most displaced and as a result, could not be clearly distinguished (contoured) on imaging studies. In this situation, it was generally possible to keep the single-session dose to the visible portions of the visual pathways to less than 5 Gy.

Radiosurgery was delivered in two to five sessions to an average target volume of 7.7 cm^3 (range, 1.21–42 cm^3) using a total marginal dose of 20.3 Gy (range, 15.0–30.0 Gy) (*Table 1*). Treatment dose was prescribed to a mean isodose line of 80% (range, 70–95%), normalized to an average maximum dose of 25.5 Gy (range, 18–43 Gy). Patients were treated with five (n = 19), four (n = 2), three (n = 17), or two sessions (n = 11). Individual sessions of radiosurgery were separated by 12 (n = 3) or 24 hours (n = 46).

Clinical Follow-up

Ophthalmic visual field examination, clinical evaluation and MRI scans were performed for all patients before treatment and at follow-up intervals of every 6 months posttreatment during the first 3 years and annually thereafter. A multidisciplinary tumor board consisting of neurosurgeons and neuroradiologists assessed radiographic imaging studies. Formal Goldman visual field testing was performed by neuro-ophthalmologists. Patients from outside centers had their clinical reports, visual fields, and radiographic studies sent to us for review, and comparisons were recorded. The formula for an idealized ellipsoid, volume = 4/3 π (length/2 $\times$ width/2 $\times$ height/2), was used to estimate relative tumor volume on pretreatment and follow-up contrast MRI scans.

TABLE 2. Biological equivalent dose values for commonly used radiosurgery dose schedules[a]

Radiosurgery schedule		BED (Gy)			
Total dose (Gy)	No. of fractions	α/β=2	α/β=3	α/β=10	Single dose equivalent (Gy, assume α/β=2)
15	1	127.5	90	37.5	15
16	1	144	101.3	41.6	16
18	1	180	126	50.3	18
20	1	220	153.3	60	20
18	2	99	72	34.2	13.1
20	2	120	86.7	42.8	14.5
22	2	143	102.7	49.0	16.0
21	3	94.5	70	35.7	12.8
24	3	120	88	43.2	14.8
21	4	76.1	57.8	34.5	11.4
25	5	87.5	66.7	40.3	12.3

[a] BED, biological equivalent dose.

RESULTS

Tumor Control

Mean radiographic followup was 46 months (range, 13–100 mo; median, 45 mo). Forty-six (94%) patients experienced either a decrease of more than

20% or stabilization (15 patients) in tumor volume throughout the course of follow-up (*Figs. 1* and *2*, *Table 3*). However, in two meningioma patients, tumor progression occurred close to or within the treatment field and eventually resulted in death. A third patient with Cushing's disease had an initial good radiographic and hormonal response to each of three radiosurgical sessions before subsequently developing further tumor recurrences, which ultimately resulted in death.

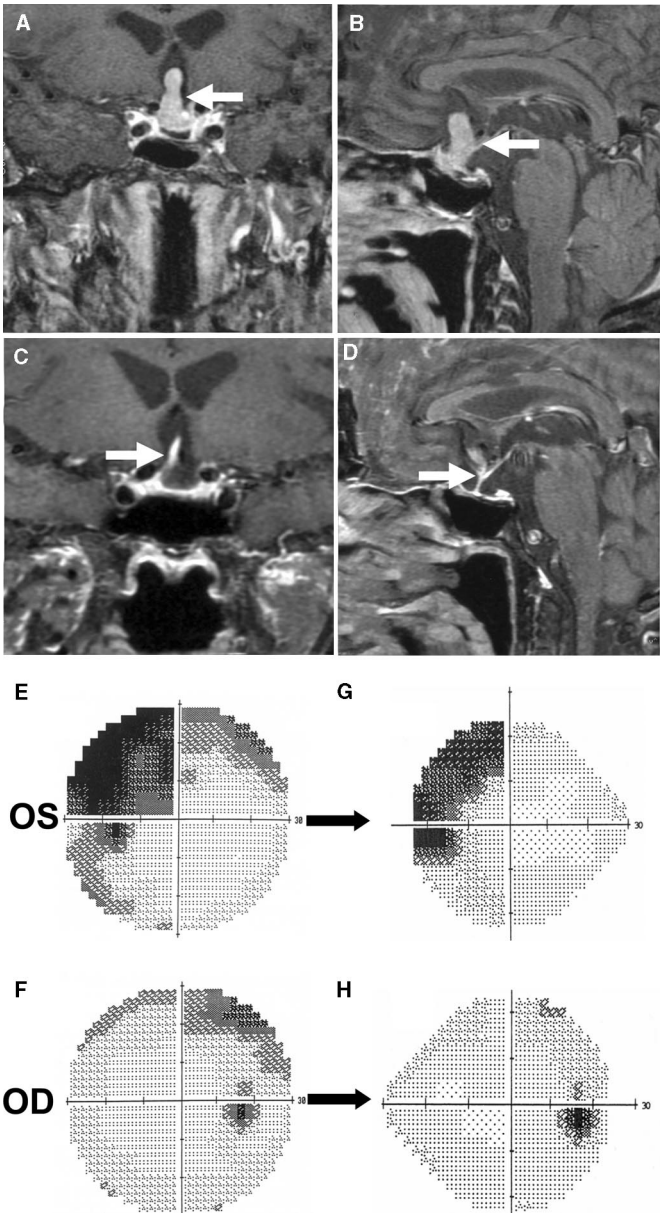

FIGURE 1. *Coronal (*A *and* C*) and sagittal (*B *and* D*) T-1 contrast MRI scans demonstrating a recurrent, nonsecreting pituitary adenoma (*arrows*) in a 67-year-old man just before (*A *and* B*) and 52 months after (*C *and* D*) multisession CyberKnife radiosurgery using a prescription dose of 24 Gy at the 85th percentile isodose line in five sessions. Bilateral visual field examination immediately before (*E *and* F*) and 53 months after (*G *and* H*) radiosurgery.*

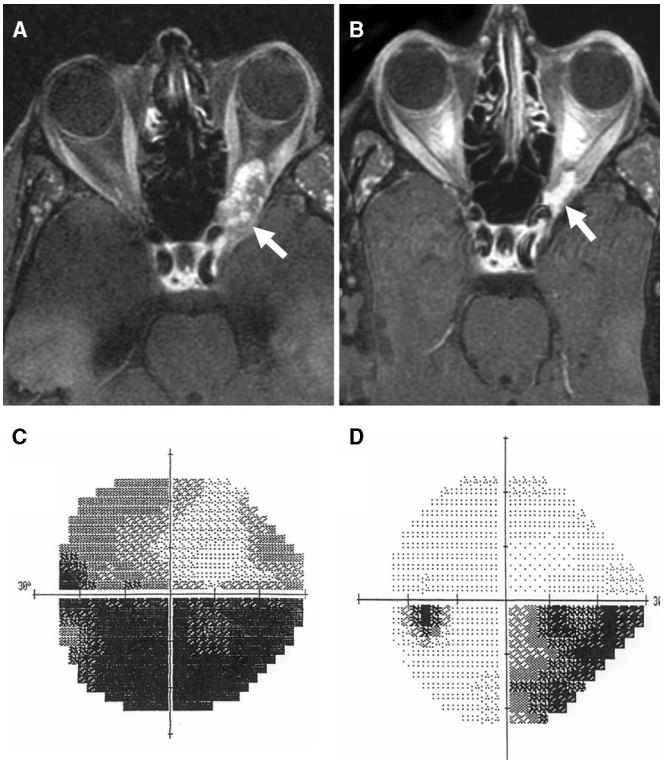

FIGURE 2. *Axial T1 contrast MRI scans demonstrating residual previously biopsied meningioma in a 46-year-old man before (*A*) and 55 months after (*B*) multisession CyberKnife radiosurgery using a prescription dose of 18 Gy at 75th percentile isodose line in five sessions. Visual field examination in the affected eye immediately before (*C*) and 54 months after (*D*) radiosurgery.*

TABLE 3. Results

Mean follow-up (visual field)	49 mo (range, 6–96 mo)
Vision, no. (%)	
Unchanged	38 (78)
Improved	8 (16)
Worse	3 (6)
Mean radiographic follow-up	46 mo
Tumor control or stabilization	46 (94%)

Vision

Mean visual field follow-up was 49 months (median, 46 mo; range, 6–96 mo). Follow-up was less than 24 months in only two cases; one of these patients (evaluated 6 mo postradiosurgery) died of pancreatic cancer 13 months after radiosurgery, whereas another, an 82-year-old woman, had an unchanged formal visual field at 18 months and subjectively stable vision after 3 years of follow-up, albeit heavily compromised by both severe macular degeneration and glaucoma.

Visual fields remained stable or improved in 46 out of 49 (94%) patients (*Table 3*). Eight of the 35 patients who had

visual field abnormalities before radiosurgery experienced significant improvements of vision. In contrast, three patients in this study experienced gross deterioration in vision, which was confirmed on formal visual testing. Two meningioma patients lost vision in the ipsilateral eye (one went on to complete blindness) in the setting of relentless and eventually fatal tumor progression. The underlying cause of blindness in both patients was simply the failure of radiosurgery to control each meningioma. However, a third case of visual loss occurred in one eye of a patient who had received a previous course of radiotherapy and three separate sessions of radiosurgery for a multiply recurrent adrenocorticotropic hormone-secreting pituitary adenoma (in 1996, 1999, and 2001). In this patient, radiation injury to the optic nerve was the presumed culprit. Subsequently, this man's pituitary tumor continued to enlarge inexorably, and he ultimately died of this lesion.

Death from Unrelated Cause

Two patients in this study died from unrelated non-brain tumor causes. A 76-year-old woman died of pancreatic cancer and an 86-year-old man died from cardiopulmonary arrest. Consequently, overall survival in this series was 90%, and disease-specific survival was 94% during the 49-month mean follow-up period.

Treatment-related Morbidity

Except for rare and fleeting headaches and an occasional complaint of transient diplopia lasting for less than 6 weeks in three patients, all of whom responded to a short course of dexamethasone, there was no acute or subacute morbidity observed during this study. The only significant long-term morbidity related to vision. In two patients, both relatively young women with "histologically benign" radiation-induced cavernous sinus meningioma, varying degrees of blindness developed over time and correlated with massive tumor regrowth after an initial period of tumor shrinkage. Only one patient in this series experienced visual loss that could be directly attributed to radiosurgery. This 49-year-old man with recurrent Cushing's disease had previously undergone multiple transsphenoidal resections, radiotherapy, and two previous courses of stereotactic radiosurgery. An MRI scan obtained before his third course of radiosurgery revealed three small foci of recurrent pituitary adenoma, one anterior and medial to the left optic nerve, a second posterior and superior to this optic nerve, and a third adjacent to the optic chiasm. In addition, the patient was severely debilitated by an associated significant increase in serum adrenocorticotropic hormone levels. During his last course of radiosurgery, each tumor foci was treated daily over a course of three sessions using a total marginal dose of 21 Gy. Six months later, this patient experienced complete loss of vision to his left eye without concomitant tumor growth on brain MRI scans. Eighteen months later, he died from a massive regrowth of his pituitary adenoma.

DISCUSSION

Despite numerous advances in imaging and operative technique, parasellar tumors remain a major neurosurgical challenge. Tumor control and binocular visual preservation continue to be the overriding concerns. By enabling acute decompression of the optic nerves and chiasm, transsphenoidal or transcranial microsurgical removal are the treatments of choice for most patients. However, many perioptic tumors involve the cavernous sinus and are not readily resectable. Some patients, by virtue of age or medical infirmity, are poor operative candidates. Whenever microsurgery is deemed inadvisable, single-session radiosurgery or conventional fractionated radiotherapy are currently the principle alternative approaches (4, 11, 45, 49).

Single-session Radiosurgery

With a 5-year tumor control rate that exceeds 90%, single-session radiosurgery is safe and effective for many parasellar lesions (12, 29, 31, 65). However, in cases in which a segment of the optic nerve or chiasm is irradiated with more than 8 to 10 Gy in a single fraction, studies demonstrate a risk of visual injury (23, 36, 71). Consequently, when the distance between tumor and anterior visual pathways is less than 3 mm, radiosurgery in which the optic apparatus typically receives more than 10 Gy is usually thought to be contraindicated. Although our understanding of the precise threshold dose of radiation that results in optic nerve or chiasm damage continues to evolve, the basic principle is widely acknowledged.

Radiation Therapy for Perioptic Tumors

Surgically unresectable benign brain tumors that are within 3 mm of or even displacing the anterior visual pathways are most commonly managed with XRT. Treatment of these lesions with doses of radiation between 45 and 55 Gy using 1.8 to 2 Gy fractions successfully prevents growth of tumor in most patients (40, 69). Long-term (10 yr) local control ranges from 68 to 89% for meningioma (5, 24, 69) and 89% for pituitary adenoma (60), but only 53% for craniopharyngioma (67). There is little doubt that radiation therapy is a powerful tool for managing many benign parasellar and cranial base lesions.

The relative safety of using radiation therapy to treat parasellar lesions is unquestioned. However, there are inherent limitations. Because of set-up inaccuracies, the treatment field includes a margin that results in the irradiation of normal structures such as the optic nerve, medial temporal lobe, hypothalamus, and pituitary gland. Although generally thought to be safe, this situation is undoubtedly responsible for the occasional occurrence of injury to the anterior visual pathways and the more common and well established association with pituitary failure (10, 18). It is worth emphasizing that optic nerve injury has been reported with even the most sophisticated and accurate of modern conventionally fractionated radiotherapy regimens (50). Much less frequently, brain necrosis and secondary malignancy formation can complicate the treat-

ment of lesions involving the parasellar region with conventionally fractionated XRT. Meanwhile, the very long-term (multiple decades) consequences of this normal, wider field irradiation, a subject of great relevance to the treatment of younger patients, remain uncharacterized.

There are additional shortcomings to conventional radiotherapy. When conventionally fractionated treatment fails the first time around to control a perioptic tumor, a second course of treatment to the recurrent lesions is almost never an option. Similarly, patients who have been previously treated with radiation therapy to an adjacent cranial base region (for another indication) are usually not eligible for a second course of irradiation to a benign perioptic tumor. A final shortcoming to standard XRT, albeit minor, is the fact that a 6-week course of therapy may be inconvenient for many patients. Although some radiation oncologists have legitimately argued that the treatment of benign brain lesions need not be rushed (13), an equally effective, yet shorter, treatment is nonetheless attractive to most patients.

Rationale for Using a Radiosurgical Technique

In contrast with spatially less accurate radiotherapy techniques, radiosurgery has the capacity to minimize the irradiation of nearby critical structures and, thereby, restrict collateral damage. This ability to limit radiation damage to normal brain anatomy would seem intrinsically desirable even if some benefits defy easy identification. This capacity could be particularly beneficial in the treatment of perioptic lesions, in which the radiation tolerance of the optic apparatus is so critical. Our experience to date, which is also mirrored by recent reports with single fraction gamma knife radiosurgery, suggests that such a "volume effect" also exists for anterior visual pathways (i.e., the radiation tolerance of the optic apparatus and chiasm is inversely proportional to the length of irradiated nerve) (42, 54). The existence of such a correspondence would not be surprising given the otherwise apparent universal nature of this radiosurgical principle throughout the rest of the brain and, perhaps, even the spinal cord (17). The "volume effect" is an important phenomenon throughout radiosurgery and is likely to have played a key role in the relative safety of the multisession radiosurgery administered in this series.

Multisession Radiosurgery

Empirically derived, fractionation is a primary cornerstone of radiation therapy. This concept allows radiation oncologists to balance the opposing objectives encountered in the treatment of tissues with markedly different responses (i.e., normal and neoplastic). The recent arrival of image-guided radiosurgical technology now makes it practical to consider incorporating the principle of multiple sessions into the delivery of radiosurgery. In doing so, this new class of treatment blends the anatomic precision and conformality of radiosurgery with the biological advantages of multiple treatments. One is no longer constrained to administer highly accurate treatments in a single session, and, at the same time, by taking advantage of the volume effect, one could, theoretically, use larger doses per session for treating perioptic neoplasms than was previously possible with conventional radiation therapy. This potential advantage provided the foundation for our use of multisession radiosurgery for managing perioptic lesions.

Why Larger Doses per Session?

Because standard radiotherapy works so well, why change the fraction size? Our earliest rationale for using multiple radiosurgery sessions rather than the standard 1.8 to 2 Gy fraction size stemmed from the limitations of frame-based targeting and first-generation image-guidance technology. However, an equally important rationale for using larger doses per session of radiation stems from basic radiobiology. Although there is no side-by-side controlled study to demonstrate the benefits of larger fraction size in treating benign as opposed to malignant brain tumors, there is a sound theoretical basis for such a conclusion (9). Meanwhile, studies comparing stereotactic radiosurgery with XRT in the treatment of benign tumors demonstrate high rates of tumor control with both modalities. Nevertheless, the larger dose per session that characterizes radiosurgery results in a higher biological equivalent dose and subsequently correlates with greater tumor shrinkage on follow-up imaging (43). Finally, larger doses per session permit the treatment to be appreciably shortened relative to radiation therapy, which, all things being equal, is desirable to most patients. With recent refinements in image-guided technology, radiosurgery is now easily administered in whatever number of sessions is biologically optimal for a specific lesion.

Clinical Outcome

The clinical series reported here was heavily selected and includes patients with several types of benign tumors, who ranged in age and in their history of previous treatment. In considering this spectrum of clinical scenarios and the slow growth of many of these benign lesions, it is dangerous to overstate the efficacy and safety of the clinical approach that we investigated. Nevertheless, the overall intermediate-term results as assessed by tumor control or shrinkage would seem to be satisfactory by most measures, especially when considering that several patients had no other treatment alternatives. Only longer follow-up periods can establish the ultimate rate of control after multisession radiosurgery.

Visual Preservation

Three patients experienced visual loss, but the loss was attributable to the radiosurgery itself in only one. This patient was unique in that he had been treated with standard radiation therapy and radiosurgery on three separate occasions before experiencing an injury to his optic nerve. Clearly, there are limitations to the amount of radiation that can be delivered safely. This particular patient was reluctantly managed with such an aggressive course of radiation

only because there were no other reasonable treatment alternatives. The loss of vision in the other two patients was caused by tumor progression. In retrospect, one of these patients clearly seems to have received a subtherapeutic dose. In the second patient, a multiply recurrent radiation-induced lesion defied repeated efforts to achieve long-term tumor control.

Although, occasionally, radiation-induced optic neuropathy has been reported to take several years to manifest, it usually presents in the first 24 months after irradiation. Consequently, the duration of follow-up in the present series provides some measure of confidence that the technique we described is reasonably safe under these circumstances; we again emphasize that the patients in this series had a relatively short segment (approximately 2 cm or less) of involved optic apparatus. It is quite possible that patients with even larger tumors with longer nerve involvement treated with multisession radiosurgery could experience visual complications.

It is possible that, with longer follow-up periods, additional patients in this series might experience visual loss as a result of radiation injury. Ove et al. (49) reported visual pathway injury occurring more than 2 years after radiosurgery. In contrast, Kondziolka et al. (32) recently reported, in a series of patients with benign tumors followed for more than 9 years, that postradiosurgery complications or tumor progression very rarely occurred beyond 3 years. Our own experience at Stanford is more consistent with Kondziolka et al.'s study. After one and a half decades and more than 3500 patients, all significant radiation injury after radiosurgery presented during the first 2 years. Consequently, we think it is improbable that there will be any major changes in the visual outcome in these patients in the coming years.

Selection of Dose and Number of Sessions

At the start of this study, we harbored grave concerns that effective multisession radiosurgical doses could prove injurious to the adjacent anterior visual pathways. Initial selection of doses and number of sessions were based largely on the senior author's (JRA) earlier experience, albeit limited, using inpatient, frame-based stereotactic targeting to administer three sessions to selected perioptic tumors that could not be managed with single-session radiosurgery. The subsequent availability of image-guided radiosurgery enabled greater flexibility in selecting a course of hypofractionation, and as the scope of this experience has grown, we became emboldened to expand its application to new indications such as ever larger lesions, resulting in ever greater effacement or obscuration of the visual pathways. Despite the relative success with small and moderate size lesions described in this report, it is possible that optic nerve injury can result if one breaches some dose per volume threshold beyond the approximate 2.0 cm (length of nerve) limit of the current series.

The current study demonstrates both the relative safety and intermediate-term efficacy of multisession radiosurgery in the management of selected perioptic lesions. However, it would be naive to suggest that the specific dose of radiation and the number of fractions used in this report represent some optimum for such tumors. It is not unreasonable that the optimal dose in individual patients may depend on a range of variables including pathology, volume of tumor, length of involved optic apparatus, history of previous surgical or irradiation intervention, patient age, specific region of visual pathway involvement, etc. Significantly, more study is needed to address these numerous variables and refine our current understanding. However, the doses and number of sessions we report here constitute useful starting points for future investigation with multisession radiosurgery. Despite the remaining uncertainties, multisession radiosurgery seems to be a useful tool for managing selected parasellar lesions that involve the visual pathways.

Limitations of the Current Study

Although multisession radiosurgery has proven relatively successful in our experience, definitive conclusions about the safety and efficacy of this technique for perioptic lesions will require further experience and follow-up, ideally in conjunction with multiple institutions. In addition, it should be emphasized that the patients in this series represent a highly selected group, the exact characteristics of which are still not crisply defined. As a result, selection bias may well be an important factor in the outcome currently being reported. Finally, key radiosurgical treatment parameters (i.e., dose to optic apparatus and length of treated nerve), values that are commonly described elsewhere in the radiosurgical literature, have yet to be rigidly defined for a multisession approach to perioptic tumors. In large part, this situation stems from our limited ability to accurately gauge dose, as is more typically done with dose-volume histograms within obscured and or displaced portions of the anterior visual pathways. Although greater experience and longer follow-up periods have the potential to significantly increase our confidence in multisession radiosurgery and better identify its limitations, it is also possible that some of the more difficult to characterize aspects of this technique will, like much of neurosurgery, remain within a realm of "the art of medicine."

SUMMARY

The present investigation confirms that multisession radiosurgery seems to be a safe and effective treatment for parasellar lesions that are in close proximity to a short segment optic chiasm and proximal optic nerves. Still, longer follow-up periods with more patients are needed to completely validate these conclusions.

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COMMENTS

The authors evaluated visual and clinical outcomes after multisession radiosurgery for tumors close to visual structures. Overall, the results of tumor control and visual preservation were good. The rate of visual decline was 6%. This study adds to the notion that tumors lying directly against the optic nerve or chiasm can be safely addressed with radiosurgery. The old adage that the tumor needs to be 3, 5, or 7 mm away from the optic nerve has not been regarded as true for some time, but, in the past, when higher tumor margin doses were thought necessary, this was recommended. However, long-term tumor control can be safely achieved with margin doses of 11 to13 Gy in a single session using optic system doses below 9 Gy. Sophisticated software platforms allow the dose to be contoured away from critical structures. Indeed, the concept of keeping the optic chiasm dose below 8 Gy may have been overly cautious and was based on little evidence. Adler et al. review the present limitations with conventional fractionated radiation therapy and argue for accurate radiosurgery of benign tumors. Such targeting is facilitated by high-resolution magnetic resonance imaging, often with fat suppression techniques.

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The treatment of sellar and juxtasellar tumors near the optic apparatus remains a significant challenge for neurosurgeons and radiation oncologists. This article represents the longest reported follow-up period of intracranial "multisession" radiosurgically treated patients (mean, 49 mo; range, 6–96 mo). At last neuroimaging follow-up examination, 63% of tumors had decreased in size by 20% or more, 31% remained stable, and 6% increased. The authors observed visual field decline and tumor-related death in 6% of the patients. The latter fact speaks to the continued seriousness of this neurosurgical problem and the need for improved treatment.

"Multisession" radiosurgery falls between standard, single-fraction radiosurgery, and image-guided stereotactic radiation therapy. Overall, the technique looks promising. However, with the introduction of new techniques in neurosurgery, enthusiasm and overuse are the norm. As the risk and benefit profile is better defined, the indications are narrowed, and the application of the technique declines to a more appropriate level. We have much to learn about "multisession" radiosurgey, including long-term (10 yr or longer) tumor control rates, risk to the optic apparatus (visual acuity and not just visual fields), risk to the carotid artery, rate of delayed hypopituitarism, risk of radiation-induced neoplasia, and risk of other cranial neuropathies. Rates of hypopituitarism, cerebrovascular accidents, and radiation-induced neoplasia seem to be higher with standard fractionation schemes (1–3).

With regard to meningioma and pituitary adenoma tumor volumes postradiosurgery, the experience at my institution has been that the longer the follow-up period, the more likely the tumor either decreases or increases in size. In the long-term, few tumors remain "stable." Dysfunction of Cranial Nerves II, III, IV, V, and VI typically occurs within 3 years of radiosurgery. However, in this series, those patients who were followed for less than 3 years may still be at risk of developing visual dysfunction and should be followed closely. In my experience, delayed tumor growth, radiation-induced neoplasia, and hypopituitarism can occur much later than 3 years after gamma knife surgery.

As a neurosurgeon, I welcome this new technique for dealing with perioptic tumors. "Multisession" radiosurgery may be appropriate for those unwilling or unable to undergo extirpation, traditional radiosurgery, or image-guided radiation therapy. With a better understanding of its risk-to-benefit ratio as afforded by this series, the indications for this technique will be better defined. Optimal treatment algorithms will only be developed if surgery, radiosurgery, and radiation therapy are studied in more detail and with open-ended follow-up periods.

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Visual field preservation is a critical issue in the treatment of perioptic meningiomas or pituitary adenomas. Evaluation of radiation tolerance of the optic apparatus after single-fraction radiosurgery has been a challenging task because radiation optic neuropathy can occur from 7 to 30 months after radiosurgery (1). A recent review of 218 patients treated with gamma knife radiosurgery showed that the risk of developing a clinically significant radiation optic neuropathy was 1.1% for patients receiving 12 Gy or less to the nerves or chiasm (2). Based on this and other literature, most centers adhere to the 8 Gy guideline for single fraction radiosurgery, whereas others treat up to 12 Gy in a small portion of the optic apparatus. In many cases, for lesions in proximity to the anterior visual pathways, a sufficient dose to the tumor cannot be achieved within these accepted guidelines for normal optic nerve tolerance, and it becomes necessary to treat perioptic lesions with either fractionated external beam radiation therapy or microsurgical approaches.

This article presents intriguing preliminary data, suggesting that fractionated radiosurgery can be performed without increased toxicity to the visual apparatus. Although the radiation tolerance of the optic structures with fractionated radiosurgery regimens remains unknown, the data shown here suggest that there may be room to escalate dose and possibly improve tumor control.

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1. Girkin C, Comey C, Lunsford L, Goodman ML, Kline LB: Radiation optic neuropathy after sterotactic radiosurgery. **Ophthalmology** 104:1634–1643, 1997.
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Adler et al. present follow-up visual field data on 49 patients with tumors situated within 2 mm of the anterior visual apparatus and treated with multifraction (2–5 sessions) radiosurgery. All but two patients had 24-month visual field follow-up examinations demonstrating a high degree of visual preservation (94%) with this treatment strategy. This is an important article that demonstrates visual preservation rates comparable to conventional fractionation strategies in a significant number of patients.

I would suggest, however, that the authors may somewhat overstate the case for CyberKnife radiosurgery. Modern, intensity modulated radiotherapy and positioning strategies (e.g., bite-plate light-emitting diode systems) provide highly conformal treatments with submillimetric positioning errors. Conventional radiotherapy, including radiosurgery, has substantially improved and remains a very viable alternative to radiosurgery, whether it is single or multiple fraction. As the authors note, more data exists for efficacy and safety in the conventionally fractionated (30 fractions) and single fraction (radiosurgery) treatment paradigms than for hypofractionated (2–5 fractions) protocols.

The authors also incorrectly state that their technique provides better homogeneity than multi-isocenter radiosurgery. Other linear accelerator systems routinely treat to the 70% isodose line because that is the isodose that provides the steepest dose gradient outside the target volume. In fact, there is very little evidence that appropriately conformal radiosurgical treatments to the 50% line (the standard gamma knife paradigm) are associated with higher complications. The argument has also been made that dose inhomogeneity, by increasing the dose within the tumor, may be beneficial. The CyberKnife provides no technical advantage in terms of homogeneity, nor has any such difference been conclusively demonstrated to be clinically important.

Finally, most radiosurgical groups switched to magnetic resonance imaging scans years ago for targeting. With some difficulty, one might identify the optic apparatus on thin-cut computed tomographic slices, but there is no doubt that the optic nerves and chiasm, as well as most other normal and abnormal brain structures, are much better seen on magnetic resonance imaging scans than on computed tomographic scans. The ability to accurately image the tumor margins and normal brain structures with magnetic resonance imaging scans is arguably one of the most significant advances in radiosurgical treatments in the past decade. Without the best possible imaging, it is not possible to generate the best possible conformal treatment plans or dose gradients away from critical structures.

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