Meningiomas are typically benign tumors that develop with an increased frequency in older patients and are more common in women. The related management goals are to minimize the chance of tumor progression or recurrence and to maintain a low rate of treatment-associated morbidity. Resection of meningiomas has been the treatment of choice since the time of Harvey Cushing. It is well established, however, that complete tumor removal is not always possible in keeping with acceptable risk, and tumor recurrence rates range from 18 to 25% at follow-up periods of 10 years even after complete macroscopic tumor removal has been demonstrated. To reduce the chance of meningioma recurrence or progression, EBRT is commonly performed as a postoperative adjunct in patients in whom tumor removal has been subtotal or in whom the meningioma is atypical or malignant. Postoperative EBRT decreases the incidence of tumor recurrence and improves PFS after subtotal meningioma resection. Over the past two decades, SRS has emerged as an alternative to resection or EBRT for an increasing number of patients with recurrent or surgically high-risk meningiomas. In this paper, the outcomes of meningioma radiosurgery will be reviewed, and management guidelines based on the current understanding of this modality will be discussed.

OBJECT

Stereotactic radiosurgery (SRS) has become an important treatment option for patients with intracranial meningiomas. The author reviews the 12-year experience at a single institution and discusses the relative strengths and weakness of this management approach.

METHODS

Between January 1990 and December 2002, 330 patients (with 356 tumors) underwent radiosurgery for intracranial meningiomas. One hundred thirty-eight patients (42%) harbored recurrent/residual tumors after having already undergone resection; 192 patients (58%) underwent radiosurgery as primary treatment. The majority of patients (70%) harbored skull base tumors. The median tumor volume was 7.3 cm³ (range 0.5–50.5 cm³). The median tumor margin dose was 16 Gy (range 12–20 Gy). In 278 patients with 297 lesions the mean clinical and imaging follow-up period was 43 months (range 2–138 months). Two hundred seventy-eight tumors (94%) remained stable or decreased in size, and 19 tumors progressed in size. Factors associated with progression were tumor histological type and prior surgery. Treatment-related complications occurred in 8% of the patients and included cranial neuropathies, symptomatic edema, cyst formation, and stenosis of the internal carotid artery. In three patients (1%) tumor dedifferentiation was noted after SRS.

CONCLUSIONS

Radiosurgical treatment of meningioma is safe and it has become the primary treatment for patients with small skull base tumors. Further study is needed to determine the long-term tumor control rates after such treatment, especially for patients treated with doses of 14 Gy or less.

KEY WORDS • brain tumor • meningioma • radiosurgery • gamma knife

Abbreviations used in this paper: EBRT = external-beam radiation therapy; ICA = internal carotid artery; MR = magnetic resonance; PFS = progression-free survival; RON = radiation optic neuropathy; SRS = stereotactic radiosurgery.
without atypical or malignant features. In 231 patients (70%) tumors involved the skull base. The most frequent tumor location was the cavernous sinus (110 cases); convexity tumors were demonstrated in only 38 patients (12%).

Radiosurgery was performed using the Leksell gamma knife (Elekta Instruments, Norcross, GA). The model U was used before March 1997, and thereafter, we have used the model B. Stereotactic MR imaging was used for dose planning unless contraindicated; in such cases, computerized tomography scanning was performed. Multiple-shot dose plans were typically created for conformal irradiation of the often irregularly shaped tumors (Fig. 1). The median number of isocenters was 10 (range one–25 isocenters). The majority of tumors were treated at the 50% isodose line. The median prescription isodose volume was 7.3 cm³ (range 0.5–50.5 cm³). Dose prescription was based on tumor size, location, and history of radiotherapy. For tumors located in sellar or parasellar regions, the dose delivered to the optic nerves or chiasm was limited to 10 Gy or less in most cases to reduce the incidence of delayed optic neuropathy. In recent years, we have determined the radiation exposure to these structures by outlining the optic apparatus and calculating the dose–volume histogram. The maximum radiation dose was defined as that received by 1% of the optic nerves and chiasm. The median tumor margin dose was 16 Gy (range 12–36 Gy). The median maximum tumor dose was 32 Gy (range 20–60 Gy).

Radiosurgery has been performed as an outpatient procedure since 1997. Following radiosurgery patients underwent follow-up evaluation and imaging at 6, 12, 24, and 48 months and then biannually thereafter. The tumor diameter in the x, y, and z planes was determined and compared with study measurements acquired on the day of radiosurgery. Tumor size was classified as unchanged, decreased, or increased. Tumor reduction was defined as a decrease in tumor size greater than 2 mm. Conversely, tumor enlargement greater than 2 mm was considered to indicate progression. Tumors demonstrating less than a 2-mm change in size were termed unchanged. In addition, the follow-up MR images were reviewed for adverse radiation-related effects, including damaged adjacent major blood vessels such as the ICA or basilar artery. All clinical and neuroimaging follow-up data were entered into our computer database. Two hundred ninety-seven tumors (278 patients) underwent clinical and imaging follow up for a mean period of 43 months (range 2–138 months) after radiosurgery. The majority of patients in whom the follow-up period was not complete were those who had undergone radiosurgery within the last 6 months; in only eight patients was no follow-up information available after radiosurgery.

RESULTS

Follow-up data were available for 267 benign tumors: 165 (62%) decreased (Fig. 2), 96 remained unchanged (36%), and six increased in size. Of note, five of the six patients with tumor progression had previously undergone surgery. In only one patient in whom radiosurgery was indicated as a primary treatment for a presumed meningioma has tumor progression been demonstrated. Follow-up imaging data were available for 30 atypical or malignant
meningiomas. Eighteen tumors (60%) decreased (eight) or remained unchanged (10). Twelve tumors (40%) enlarged after radiosurgery. Tumor progression in these 18 patients was classified as infield (seven cases), marginal (three cases), infield and marginal (one case), distant (six cases), and marginal and distant (one case).

Investigators at our center previously published a detailed analysis of 190 consecutive patients with 206 meningiomas who underwent radiosurgery between 1990 and 1998. At 5 and 7 years patient survival for the entire cohort was 82 and 82%, respectively; cause-specific survival was 94 and 92%, respectively. The cause-specific survival in patients with benign, atypical, and malignant tumors at 5 years was 100, 76, and 0%, respectively (p < 0.0001). The tumor control rate was 89%, and this correlated with tumor histological type (p < 0.0001); the 5-year control rate in patients with benign tumors was 93%, whereas it was 68 and 0%, respectively, in patients with atypical and malignant meningiomas. No correlation was found between radiation dose and tumor control.

In 26 patients (8.4%) treatment-related complications developed after radiosurgery. Cranial nerve deficits were the most common complication affecting 17 patients (6.4%). Four patients suffered neuropathies affecting multiple cranial nerves. In decreasing frequency, the cranial nerves affected were the trigeminal (10), abducens (three), optic (two), oculomotor (two), facial (two), and vestibulocochlear (two). The median time to onset of cranial nerve deficits was 6 months (range 1–98 months). At last follow-up, status in 14 patients was unchanged, and complete resolution was demonstrated in three. In five patients symptomatic brain edema developed (1.9%); all five had undergone prior surgery and two had received EBRT either before or after radiosurgery. The three patients not receiving EBRT all recovered, whereas the two patients who underwent both radiosurgery and EBRT have suffered progressive neurological decline. In two patients ICA stenosis of the cavernous segment was noted 5 years after gamma knife surgery. In the second patient a cerebral infarct occurred 35 months after SRS and occlusion of the cavernous ICA was noted. The calculated radiation dose exceeded 25 Gy to the affected arteries. In two patients cysts developed adjacent to the treated tumors 2 years after radiosurgery. One patient underwent resection of the tumor and adjacent cyst; in the other patient a cystoperitoneal shunt was placed. No new surgery-related deficits developed in either patient.

There were also three patients with tumor dedifferentiation that developed after radiosurgery (Figs. 3 and 4). One patient was a 42-year-old man in whom meningioma recurred after prior gross-total resection. The patient was treated with both radiosurgery and EBRT (45 Gy). Four and half years after radiosurgery and EBRT, the tumor increased in size and repeated resection was performed. The tumor exhibited atypical features. The second patient was a 62-year-old man in whom a left falk meningioma recurred 8 years after surgery. The pathological diagnosis at the initial surgery was meningioma. Three years after radiosurgery the patient exhibited increased focal motor seizures and MR imaging demonstrated tumor enlargement. The patient underwent repeated resection. The pathological examination then showed atypical meningioma. The third patient was a 74-year-old woman with a recurrent falk atypical meningioma who underwent radiosurgery 10 months after surgery. Four years after radiosurgery the tumor enlarged and the patient required repeated surgery. The tumor was then diagnosed as a malignant meningioma. Despite postoperative EBRT (50.4 Gy), new areas of tumor developed and the patient required a second radiosurgical procedure.

**DISCUSSION**

For more than 50 years, tumor excision has been the treatment of choice for patients with intracranial meningiomas. The paper published by Simpson in 1957 showed the correlation between the degree of meningioma resection and the risk of recurrence. He noted a rate of symptomatic tumor recurrence of 9, 19, and 29% in patients who underwent Grades 1, 2, and 3 resections, respectively. Based on these findings, the basic tenet of meningioma management became surgical treatment should be aimed at complete tumor removal as well as the adjacent dura and involved bone. Improved anesthetic, neuroimaging, and microsurgical techniques have increased the number of patients in whom complete resection of meningiomas has been possible in conjunction with acceptable morbidity. Some meningiomas, however, invade adjacent neurovascular structures and simply cannot be completely excised without posing unacceptable risk. Investigators of recent series on meningioma surgery have reported that gross-total resection is possible in 38 to 100% of patients, depending primarily on tumor location. Even when a gross-total resection has been achieved, however, tumor recurrence rates can range from 18 to 25% at 10 years. The impact of subtotal resection (Simpson grade ≥ 3) on this population is even more significant. Jung, et al., reported a 5-year tumor progression rate of 40% in patients in whom petroclival meningiomas were subtotally resected. The rate of tumor growth in that series was 4 mm annually. Klink, et al., noted that 18 (62%) of 29 patients undergoing “non-radical” surgery of parasellar and cavernous sinus menin-
gions suffered tumor recurrence/progression within a mean follow-up interval of 13.6 years. The tumor progression rate in patients followed more than 15 years was 89% (eight of nine patients). Kallio, et al.,23 found the relative risk of death due to subtotal resection was nearly equal (4.2-fold greater) to the risk in patients with atypical or malignant meningiomas in their review of 935 patients.

To reduce the chance of meningioma recurrence or progression, EBRT is frequently used as a postoperative adjuvant in patients with subtotally excised tumors or in those whose tumor displayed either atypical or malignant features. Numerous studies have documented that postoperative radiotherapy decreases the incidence of tumor recurrence and improves survival for patients after subtotal meningioma resection.6,8,18,35 Moreover, selected patients have been managed with EBRT alone if they were considered medically unfit for surgery or if their tumor was deemed unresectable. Dufour, et al.,14 reported a 93% PFS rate at 10 years for 31 patients with cavernous sinus meningiomas in whom radiotherapy alone or subtotal resection was performed. In the series by Goldsmith, et al.,18 the 5-year PFS rate in patients treated with EBRT after 1980 was 98%. Despite improving survival in selected patients with meningioma, however, EBRT has been associated with long-term complications such as cognitive decline, radiation-induced neoplasms, and pituitary insufficiency.2,9

Over the past two decades, radiosurgery has been conducted as an alternative to surgery and EBRT in patients with meningiomas who have symptoms from mass effect. The tumor control rate, complications, and outcomes of our patients are quite similar to those reported in recent papers on radiosurgery for meningioma. At last follow-up, examination more than 80% of our patients were either improved or clinically stable. In a paper on patients with benign meningiomas, Kondziolka, et al.,21 reported that 91% remained neurologically stable at 5- to 10-year follow-up after radiosurgery. Tumor control rates have ranged from 84 to 100% after either gamma knife surgery and linear accelerator–based radiosurgery. Two factors have contributed to treatment-related failures after meningioma radiosurgery. First, tumor progression outside the prescription isodose volume (marginal or distant recurrences) has been well described. Kondziolka, et al.,26 found that 22 (11%) of 203 patients with parasagittal meningiomas experienced tumor progression after radiosurgery, and the authors noted 5-year actuarial control rate of 67%. If the patients with marginal or distant recurrences are excluded, the 5-year local control rate was 85%. Hakim, et al.,19 reported tumor progression in 20 (16%) of 127 patients at a median of 20 months after radiosurgery; only four treatment-related failures (3%) occurred in cases involving previously treated tumors. Analysis of such failed cases emphasizes the fact that radiosurgery is limited to controlling local disease that can be demonstrated clearly on imaging studies at the time of dose planning. Therefore, radiosurgery performed as a primary procedure may produce better tumor control rates than after previous surgery. Kondziolka, et al.,26 reported an improved 5-year actuarial tumor control rate in patients without prior surgery (93 compared with 60%); however, the difference did not reach statistical significance (p = 0.08).

Tumor histological type is the other factor associated with failed meningioma radiosurgery. The 5-year cause-specific survival in patients with benign meningiomas in our series was 100%, whereas that in patients with atypical meningiomas was 83%.30 At our center no patient with a malignant meningioma has survived 5 years after radiosurgery. The correlation between meningioma grade and radiosurgical success has been noted at other centers. The 4-year actuarial survival in patients with atypical and malignant meningiomas was 83 and 22%, respectively, in the series reported by Hakim, et al.,19 Ojemann, et al.,30 reported 22 patients with malignant meningiomas treated ra-
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diagnostically between 1991 and 1999. Disease progressed in 19 patients despite receiving prior EBRT (median dose 55 Gy). The 5-year survival and PFS were 40 and 26%, respectively. In five patients (23%) radiation necrosis developed after radiosurgery in that series. Four patients were symptomatic and three required additional surgery to control symptomatic mass effect. Consequently, it may be necessary to prescribe higher radiation doses to achieve tumor control in patients with atypical or malignant meningiomas compared with those harboring benign meningiomas. Because nearly all patients with atypical or malignant meningiomas have undergone EBRT in the past or because it is administered concurrently with radiosurgery, however, the incidence of symptomatic radiation necrosis may limit radiosurgery’s overall efficacy in this difficult patient group.

Radiation-related complications after treatment of meningioma are uncommon. Because the majority of patients harbor tumors involving the skull base, cranial neuropathies remain the most frequent source of morbidity after radiosurgery for meningioma. The special sensory nerves (optic, vestibulocochlear) appear to be the most radiosensitive. Although most centers limit the radiation dose to 8 Gy or less to minimize the chance of RON after radiosurgery, some authors believe that this estimate is too conservative and that the optic nerves and chiasm will tolerate higher radiation doses. Leber, et al., reviewed cases in which radiosurgery was used in the treatment of cavernous sinus and parasellar region lesions and found no cases of optic neuropathy in 31 patients in whom doses were as high as 10 Gy. We recently completed a detailed analysis of optic nerve tolerance in 215 patients with benign tumors adjacent to the optic apparatus. Four patients (1.9%) developed RON at a median of 31 months after radiosurgery. The risk of developing a clinically significant RON was 1.1% for patients receiving 12 Gy or less. In patients who underwent prior or concurrent EBRT there was a greater risk of developing RON after radiosurgery (p = 0.004). Therefore, fewer than 2% of our patients suffered RON despite that the majority (73%) received more than 8 Gy to a short segment of the optic apparatus. We have not performed radiosurgery in patients with optic nerve sheath meningiomas. Recent work has suggested that stereotactic radiotherapy effectively halts tumor growth and that the risk of optic nerve injury is low. We continue to recommend resection for patients with sellar or parasellar meningiomas and visual deficits. Decompression of the optic structures frequently restores visual function and should be considered the best treatment for these patients.

Radiosurgery has been particularly effective in the management of patients with cavernous sinus meningiomas. Although some authors in the past have argued that aggressive resection is not only possible but also desirable for these tumors, it is now recognized at most centers that radiosurgery is the preferred modality for this group of patients with meningioma. Over the past several years, the results obtained in more than 500 patients have been reported after radiosurgical treatment of cavernous sinus meningiomas. The median tumor margin dose in these series was between 13 and 14 Gy. Progression-free survival rates of 93 to 100% have been noted at median follow-up periods of up to 49 months. The complication rates ranged from 3 to 10%, with many of these being temporary cranial nerve deficits that improved over time. Based on these results, unless the patient harbors a large tumor causing mass effect in the middle or posterior fossa, radiosurgery can be safely and effectively performed as the primary treatment in patients with cavernous sinus meningiomas.

We recently conducted a study comparing resection and radiosurgery as the primary management in adult patients with benign meningiomas (mean tumor diameter < 35 mm). Between 1990 and 1997, 198 patients meeting these criteria were enrolled, and data were analyzed for tumor recurrence or progression. The mean follow-up period was 64 months. Tumor resections stratified by Simpson grade were Grade 1, 57 patients (42%); Grade 2, 57 patients (42%); and Grade 3 to 4, 22 patients (16%). The mean margin and maximum radiation doses at radiosurgery were 17.7 and 34.9 Gy, respectively. Tumor recurrence/progression was more frequent in the surgical resection group (12%) than the radiosurgical group (2%) (p = 0.04). No difference was detected in the 3- and 7-year actuarial PFS in patients with Simpson Grade 1 resections (100 and 96%, respectively) or radiosurgery (100 and 95%, respectively) (p = 0.94). Radiosurgery provided a higher PFS rate than Simpson Grade 2 resection (3- and 7-year PFS, 91 and 82%, respectively; p < 0.05) or Grade 3/4 resection (3- and 7-year PFS, 68 and 34%, respectively; p < 0.001). Subsequent tumor treatments were more common after resection (15 and 3%, respectively; p = 0.02). Complications occurred in 10% of radiosurgery-treated patients and 22% of surgery-treated patients (p = 0.06). Therefore, in this study, the radiosurgery-related PFS rate was equivalent to that of Simpson Grade 1 resection, whereas it was superior to Grades 2 and 3/4 resections. Thus, if long-term follow-up data confirm the high tumor control rate, this technique will likely become the preferred treatment for the majority of patients with small- to moderate-sized meningiomas without symptomatic mass effect.

Several factors must be remembered when discussing the present results of meningioma radiosurgery. First, a minimum follow-up period of 10 years is needed to allow adequate assessment of any technique used to manage patients with meningioma. Presently, the best available data are derived from 5- to 10-year follow-up periods after radiosurgery. Second, resection remains the best treatment in patients with tumors located in regions where a complete resection (Simpson Grade 1) is possible. Kinjo, et al., reported no surgery-induced morbidity and found no tumor recurrence in a series of 37 patients harboring convexity meningiomas. Thus, in cases in which radical resection of a meningioma can be performed with minimal risk, it should be performed to avoid the risk of delayed radiation-related complications. Third, delayed complications after radiosurgery are now being described and include injury to large intracranial arteries and cyst formation. Symptomatic ICA injury developed in two patients in whom cavernous sinus meningiomas were treated radiosurgically at our center to date. Both patients suffered permanent neurological deficits secondary to ischemic events. Roche, et al., reported on a patient in whom a temporary central facial palsy developed 14 months after radiosurgical treatment of a cavernous sinus meningioma.
meningioma and was discovered to have occlusion of her intracavernous ICA. Attention is now paid to minimizing the radiation dose to major arteries at the time of radiosurgery. In our series there have been two cases of symptomatic cysts developing adjacent to the irradiated tumors, which required surgical decompression. This complication has been described after radiosurgery for arteriovenous malformation and is thought to be due to a breakdown of the blood–brain barrier adjacent to the irradiated lesion.5,54 Again, limiting the radiation exposure of the adjacent brain parenchyma by using conformal radiation delivery is a likely strategy to minimize the risk of this complication. Fourth, as more patients undergo radiosurgery based on neuroimaging data alone without histological confirmation, a small percentage will actually harbor other tumor types (hemangiopericytoma, chordoma) or potentially nonneoplastic lesions such as sarcoidosis.53 Last, there is the chance that tumors may dedifferentiate (malignant transformation) or radiation-induced tumors that may develop after radiosurgery. In our series, three patients suffered tumor dedifferentiation, and repeated surgery was required. Although dedifferentiation of meningiomas has been noted in patients after surgery alone,59 malignant transformation has been reported after vestibular schwannoma radiosurgery.46 Radiation-induced neoplasms have now been reported after radiosurgical treatment of meningiomas.55 Vestibular schwannomas,44 and arteriovenous malformations,22 Although we do not know the actual risk of this complication, current estimates would place the risk much lower than the 1 to 3% typically quoted after fractionated radiotherapy. To overemphasize the risk of radiation-induced neoplasms developing after radiosurgery is inappropriate when discussing this treatment option with patients.

References