Radiosurgery as Definitive Management of Intracranial Meningiomas

Objective: Stereotactic radiosurgery has become an important primary or adjuvant minimally invasive management strategy for patients with intracranial meningiomas with the goals of long-term tumor growth prevention and maintenance of patient neurological function. We evaluated clinical and imaging outcomes of meningiomas stratified by histological tumor grade.

Methods: The patient cohort consisted of 972 patients with 1045 intracranial meningiomas managed during an 18-year period. The series included 70% women, 49% of whom had undergone a previous resection and 5% of whom had received previous fractionated radiation therapy. Tumor locations included middle fossa (n = 351), posterior fossa (n = 307), convexity (n = 126), anterior fossa (n = 88), parasagittal region (n = 113), or other (n = 115).

Results: The overall control rate for patients with benign meningiomas (World Health Organization Grade I) was 93%. In those without previous histological confirmation (n = 482), tumor control was 97%. However, for patients with World Health Organization Grade II and III tumors, tumor control was 50 and 17%, respectively. Delayed resection after radiosurgery was necessary in 51 patients (5%) at a mean of 35 months. After 10 years, Grade I tumors were controlled in 91% (n = 53); in those without histology, 95% (n = 22) were controlled. None of the patients developed a radiation-induced tumor. The overall morbidity rate was 7.7%. Symptomatic peritumoral imaging changes developed in 4% of the patients at a mean of 8 months.

Conclusion: Stereotactic radiosurgery provided high rates of tumor growth control or regression in patients with benign meningiomas with low risk. This study confirms the role of radiosurgery as an effective management choice for patients with small to medium-sized symptomatic, newly diagnosed or recurrent meningiomas of the brain.

Key Words: Brain tumor, Meningioma, Radiosurgery
TABLE 1. Locations of 1045 intracranial meningiomas

<table>
<thead>
<tr>
<th>Location</th>
<th>No. of tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior fossa</td>
<td></td>
</tr>
<tr>
<td>Petroclival</td>
<td>122</td>
</tr>
<tr>
<td>Petrous ridge</td>
<td>66</td>
</tr>
<tr>
<td>Foramen magnum</td>
<td>22</td>
</tr>
<tr>
<td>Other</td>
<td>42</td>
</tr>
<tr>
<td>Middle fossa</td>
<td></td>
</tr>
<tr>
<td>Cavernous sinus</td>
<td>306</td>
</tr>
<tr>
<td>Sphenoid wing</td>
<td>32</td>
</tr>
<tr>
<td>Other</td>
<td>13</td>
</tr>
<tr>
<td>Anterior fossa</td>
<td></td>
</tr>
<tr>
<td>Olfactory groove</td>
<td>29</td>
</tr>
<tr>
<td>Planum sphenoidale</td>
<td>29</td>
</tr>
<tr>
<td>Anterior clinoid</td>
<td>17</td>
</tr>
<tr>
<td>Parasellar</td>
<td>13</td>
</tr>
<tr>
<td>Convexity</td>
<td>126</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Parasagittal</td>
<td>113</td>
</tr>
<tr>
<td>Tentorial notch</td>
<td>40</td>
</tr>
<tr>
<td>Torcular</td>
<td>6</td>
</tr>
<tr>
<td>Falcine</td>
<td>47</td>
</tr>
<tr>
<td>Intraorbital</td>
<td>13</td>
</tr>
<tr>
<td>Intraventricular</td>
<td>9</td>
</tr>
</tbody>
</table>

RESULTS

Imaging studies after radiosurgery showed that 407 tumors had regressed, 454 were unchanged, and 96 had enlarged, for a raw tumor control rate of 90%. Actuarial tumor control, survival, and disease-specific survival by World Health Organization (WHO) grade are shown in Figures 1-3. Imaging and clinical follow-up was requested for all patients, but was not complete for all.

Adjuvant Radiosurgery

Based on previous histopathology, we had 424 WHO Grade I meningiomas in this series, 384 of which were available for study. We found that 172 tumors had regressed, 186 were unchanged, and 26 had enlarged, for a tumor control rate of 93% at a median of 4 years. Ninety-one percent of the patients were either clinically improved (n = 21) or unchanged (n = 341). Imaging follow-up past 8 and 10 years was obtained in 79 and 53 tumors, respectively, both with a control rate of 91% (Figs. 4 and 5). Past ten years, 45 patients were stable, six were improved, and two were worse. For Grade I meningiomas, the 5-, 10-, and 15-year actuarial tumor control rates were 97 ± 1.2, 87.2 ± 4.4, and 87.2 ± 4.4%, respectively. Disease specific survival was 98.9 ± 0.5, 96.2 ± 1.9, and 96.2 ± 1.9%, respectively.
Of 56 WHO Grade II tumors, 54 were available for review. Sixteen had regressed, 11 were unchanged, and 27 had enlarged, resulting in a tumor control rate of 50% at a median of 2 years. During the follow-up period, 72% of these patients were stable clinically. Of 31 WHO Grade III tumors, 29 were reviewed. We found that four regressed, one was stable, and 24 later enlarged, resulting in a tumor control rate of 17% at a median of 15 months.

**Primary Radiosurgery**

There were 536 tumors that received radiosurgery as primary management without previous histological confirmation. All patients had typical contrast-enhancing, dural based tumors. We were able to evaluate later serial images for 488 tumors. We found that 215 tumors had regressed, 256 were unchanged, and 19 had enlarged, resulting in a tumor control rate of 97% at a median of 4 years. Ninety-three percent of patients with these tumors either improved neurologically (n = 87) or remained unchanged (n = 380). There was no difference in the tumor response between male and female patients. Follow-up imaging past 8 and 10 years was obtained in 49 and 22 tumors, respectively, with control rates of 94 and 95%. Past 10 years, 16 patients were stable, three were improved, and three were worse. When recurrence after primary radiosurgery did occur, it was not typically from the contrast-enhancing dural tail adjacent to many meningiomas, particularly at the cranial base.

Subsequent surgical resection was performed in 51 patients (5.2%) due to local tumor growth or increased symptoms at an average time of 35 months. Additional fractionated radiotherapy was used in 2.9% at an average of 32 months. Further radiosurgery was performed in 41 patients (4%), usually for new tumors, at an average of 49 months. Eight patients later received chemotherapy (0.8%). None of the patients developed a radiation-induced tumor.

**Complications**

After radiosurgery, all patients returned to their preoperative activities immediately. After radiosurgery, nausea or other immediate symptoms were rare. One patient developed pneumonia 1 week after radiosurgery and died. A complication attributed to radiosurgery was observed in 76 patients (7.7%) at an average time of 11 months. The morbidity rates for cavernous sinus location and parasagittal locations were 6.3 and 9.7%, respectively. For cavernous sinus tumors, these included cranial nerve deficits in 12 patients. Four of these had diplopia, and two had trigeminal neuropathy (one of whom had neuralgic pain). Six patients...
had decreased visual acuity, four of whom had previous treatment that included multiple resections (n = 3), multiple radiosurgeries (2), radiation therapy (n = 3), and chemotherapy (n = 1).

The 10- and 15-year actuarial complication rates were both 9.1%. Specifically, hydrocephalus was found in 0.4%, a cranial nerve deficit in 3.4%, headaches in 2.2%, seizures in 2.4%, a motor deficit in 1.4%, and a sensory deficit in 0.3%. A ventriculoperitoneal shunt was placed in five patients (0.5%) at an average of 20 months. Complete resolution of symptoms was noted in 35% of patients who sustained morbidity. Imaging showed interval development of tumoral signal abnormalities determined by long relaxation time magnetic resonance imaging scans in 6.2% of the patients, with 4% of the total series having symptomatic imaging changes at an average of 8 months.

**Multivariate Analyses**

The results of multivariate analyses of survival, disease-free survival, and local control are shown in Table 2. Worse overall survival significantly correlated with increasing age ($P = 1.206 \times 10^{-20}$ hazard ratio [HRR] = 1.073 per year [95% confidence interval, 1.057–1.089 per yr]), increasing WHO Grade 0 to III (0 for no tissue diagnosis) ($P = 3.9385 \times 10^{-31}$, HRR = 2.002 [1.629–2.460] per grade), and increasing volume ($P = 0.0407$, HRR = 1.0416 [1.022–1.062] per cm$^3$). Worse disease-specific survival correlated with WHO Grade 0 to III ($P = 6.138 \times 10^{-25}$, HRR = 5.910 [4.217–8.284] per grade), increasing age ($P = 0.001528$, HRR = 1.045 [1.016–1.074] per year), and with multiple meningiomas ($P = 0.02754$, HRR = 2.208 [1.092–4.465]. Poorer intracranial tumor control correlated with increasing WHO Grade 0 to III ($P = 5.236 \times 10^{-27}$, HRR = 3.962 [3.084–5.093] per grade), increasing volume ($P = 0.1190$, HRR = 1.030 [1.007–1.054] per cm$^3$), and with multiple meningiomas ($P = 0.03589$, HRR = 1.782 [1.039–3.058]. The actuarial plots for intracranial tumor control and disease-specific survival according to WHO grade are shown in Figures 1 and 2.

Univariate and multivariate analyses of postradiosurgery complications and new T2-weighted imaging changes are shown in Table 3. Both volume and 12-Gy volume significantly correlated with the development of postradiosurgery complications and new T2-weighted changes in univariate testing ($P < 0.0001$), whereas in multivariate analysis, volume correlated with complications ($P = 5.268 \times 10^{-27}$, HRR = 1.068 [1.041–1.095] per cm$^3$) and 12-Gy correlated with new T2-weighted changes volume ($P = 4.066 \times 10^{-6}$, HRR = 1.057 [1.032–1.083] per cm$^3$).

**DISCUSSION**

**Indications for Radiosurgery**

Over the past two decades, the indications for meningioma radiosurgery have expanded to patients with newly diagnosed tumor as opposed to recurrent or residual tumors after initial resection (2, 4, 5, 7, 9, 12–15, 17–19, 24–26, 28, 31, 32). Those patients undergoing primary radiosurgery had imaging find-
ings that were typical of a meningioma. In long-term follow-up evaluation, we found that the initial imaging-based diagnosis of a benign meningioma was in error in 2.3%, usually proven to be a higher grade meningioma (6). As primary management, radiosurgery is not appropriate for patients with large meningiomas, for patients with significant symptomatic mass effect, and for patients with optic nerve sheath tumors and preserved vision. Although some surgeons advocate tumor debulking in symptomatic patients who are then simply followed to see if the residual tumor enlarges, the literature substantiates high recurrence and progression rates after such management. Condra et al. (3) found a 70% rate of tumor progression after subtotal resection without fractionated radiation therapy. Other groups have noted the value of postresection irradiation (8, 21). A recent series found a 4 mm mean annual rate of tumor growth after partial resection of a basal meningioma (10). We advocate that the entire neoplasm be treated using the most appropriate modalities, when safe and feasible, including complete resection, resection plus radiosurgery for residual tumors, or radiosurgery alone for small volume tumors in critical locations. We believe that this strategy will provide better long term outcomes than managing only a portion of the tumor. For these reasons, we explored the role of radiosurgery for patients with tumors in locations not amenable to surgical cure, locations at high risk for neurological deficits, those with residual or recurrent tumors, and those with growing tumors and adverse medical risk factors for resection.

Radiosurgery was thought to have only an adjuvant role for patients with “resectable” meningiomas located in convexity, falxine, or anterior fossa regions. However, patients with tumors in such locations often choose radiosurgery. Although retrospective, we believe that our patient series proposes radiosurgery as an effective and safe option for such patients. Donald Simpson’s (30) landmark article described meningioma recurrence rates based on the degree and description of the resection. He reported a 9% recurrence rate after complete resection of the tumor and its neoplastic dural base, a 19% recurrence rate when the tumor was resected and the dural base only coagulated, a 29% recurrence rate when the tumor itself was removed but the dural could not be excised or cauterized, and an approximate 40% recurrence rate when only a subtotal resection was performed. In the modern era, even higher recurrence rates have been reported (29). Pollock et al. (27) studied 136 patients after resection and 62 after radiosurgery with a mean follow-up period of 64 months. Their recurrence rates after resection were remarkably similar to the findings of Simpson more than 40 years earlier. Tumor recurrence was more frequent in the resection group (12 versus 2%; P = 0.04). There was no difference in recurrence rates for patients after a Simpson Grade I resection, but radiosurgery provided more durable control after Grade II resection (P = 0.05) or Grades III to IV resections (P < 0.001) (27). Thus, one could conclude that the results of radiosurgery for a smaller tumor are equal to or better than after a resection, depending on the degree of resection expected.

In a previous review of 5- to 10-year outcomes in 99 patients, we surveyed patients for their own opinions regarding outcomes (14). Sixty-five patients answered our questions regarding employment. Twenty-seven patients (42%) were employed at the time of radiosurgery and 20 remained so (74%). Of 35 patients not employed at radiosurgery, five (14%) resumed employment. Patients described their overall level of activity as remaining unchanged in 65%, being increased in 8%, or decreased in 27%. Radiosurgery was described as a “successful” treatment by 67 out of 70 patients (96%) (14). Patients undergoing outpatient radiosurgery have not been exposed to the risks related to an open surgical exposure, brain retraction, anesthesia, or a prolonged hospital stay.

Long-term Expectations

How long should such tumors be followed with serial imaging? After 10 years, we request an imaging assessment every 4

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**TABLE 3. Uni- and multivariate analyses of the probability developing symptomatic complications or new imaging changes after meningioma radiosurgery**

<table>
<thead>
<tr>
<th>Variable</th>
<th>P value, complications (univariate)</th>
<th>P value, complications (multivariate)</th>
<th>P value, T2-weighted imaging changes (univariate)</th>
<th>P value, T2-weighted imaging changes (multivariate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>5.268E-07</td>
<td>5.268E-07</td>
<td>1.048E-05</td>
<td>0.7159</td>
</tr>
<tr>
<td>12-Gy volume</td>
<td>4.141E-06</td>
<td>0.3558</td>
<td>2.881E-06</td>
<td>4.066E-06</td>
</tr>
<tr>
<td>WHO grade</td>
<td>0.05634</td>
<td>0.8812</td>
<td>0.2352</td>
<td>0.5487</td>
</tr>
<tr>
<td>Age</td>
<td>0.06807</td>
<td>0.1895</td>
<td>0.03551</td>
<td>0.0682</td>
</tr>
<tr>
<td>Sex</td>
<td>0.2403</td>
<td>0.7250</td>
<td>0.3730</td>
<td>0.981</td>
</tr>
<tr>
<td>Isocenters</td>
<td>0.2557</td>
<td>0.5142</td>
<td>0.6801</td>
<td>0.0826</td>
</tr>
<tr>
<td>Marginal dose</td>
<td>0.2623</td>
<td>0.9477</td>
<td>0.8156</td>
<td>0.5755</td>
</tr>
<tr>
<td>Maximum dose</td>
<td>0.5015</td>
<td>0.7307</td>
<td>0.4134</td>
<td>0.5436</td>
</tr>
<tr>
<td>Isodose</td>
<td>0.6356</td>
<td>0.2975</td>
<td>0.2045</td>
<td>0.7952</td>
</tr>
</tbody>
</table>

*WHO, World Health Organization.
In conclusion, stereotactic radiosurgery is a powerful biological approach for a patient with an intracranial meningioma that is well tolerated and can be performed on an outpatient basis. Excellent long-term outcomes can be expected in the majority of patients. In this large series of selected patients, the tumor response after radiosurgery for a primary or histologically confirmed benign tumor was as good as or better than that expected after any degree of resection. Radiosurgery should be considered an effective management choice for patients with smaller tumors, particularly in critical brain locations.

REFERENCES


Acknowledgments
We thank the staff of the Center for Image-guided Neurosurgery, whose diligent work enabled the care of patients in this study: Douglas Kondziolka, M.D., M.Sc., L. Dade Lunsford, M.D., and Ajay Niranj an, M.Ch., have a consulting agreement with Elekta Instruments, Inc.

COMMENTS
Kondziolka et al. have presented another landmark radiosurgery article that documents a very large experience with meningiomas. Over the course of 18 years, 972 patients were treated. The overall control rate for benign meningiomas was 93%. Notably, control rates for
Atypical and malignant meningiomas are much worse. These lesions will frequently recur despite maximal surgery, conventional radiotherapy, and/or radiosurgery. Overall morbidity was 7.7%, and no radiation-induced tumor has occurred. I agree that this study confirms the role of radiosurgery as an effective management choice for many meningiomas.

William A. Friedman
Gainesville, Florida

This is a retrospective review of patients with meningiomas (at all sites) who were treated with stereotactic radiosurgery at a single institution. The article is well written and includes a large number of patients who were treated by this very strong Pittsburgh group. It is already well known that radiosurgery is effective against meningiomas, and this modality is commonly used in the treatment of these tumors. The control rates and the median follow-up periods cited are in line with previous reports.

The strength of this article is the sample number; however, in gaining these numbers, Kondziolka et al. lumped meningiomas from all sites. Each meningioma site (e.g., cavernous versus convexity versus tuberculum sellae) is almost like a separate disease, with a different natural history, a different set of potential complications, and, consequently, a distinct treatment paradigm. The authors extrapolate carelessly from this massed data to conclude that radiosurgery should be considered an effective choice in the management of meningiomas. I do not think anyone could disagree with this statement at this stage in the evolution of this powerful technique.

Philip H. Gutin
New York, New York

In this article, Kondziolka et al. present a comprehensive analysis of the safety and efficacy of gamma knife surgery for the treatment of meningiomas. As neurosurgeons, we must keep in mind that the interests of all patients may not be best served by a gross total resection. Rather, in many instances (e.g., cavernous sinus meningiomas), the tumor control that is achieved by radiosurgery may afford optimal neurological function and quality of life for the patient. In this regard, the overall control rate of 93% for the larger cohort of World Health Organization (WHO) Grade I meningioma patients demonstrates the merits of a stereotactic radiosurgical approach. The authors also note a morbidity rate of 7.7%, including a 3.4% rate of cranial nerve deficit. As such, the benefit-to-risk profile of stereotactic radiosurgery for WHO Grade I meningiomas is acceptable. For WHO Grade II and III meningiomas, the reported results indicate room for improvement. Radiosurgery should not be unduly criticized for diminished efficacy in higher-grade meningiomas, as the same is true for microsurgery and radiation therapy.

This study clearly indicates that gamma knife surgery alters the natural history of most meningiomas. Moreover, the response seems durable. Failure, if it is going to occur, typically does so within the first 3 years after radiosurgery.

All neurosurgeons must continue to hone their microsurgical skills. Whenever possible, gross total resection of a meningioma should remain the goal, provided that it can be achieved with comparable or lower morbidity and mortality to radiosurgery. However, when this is not possible, a subtotal resection followed by radiosurgery or upfront radiosurgery should be used. For WHO Grade I meningiomas in particular, we cannot make the “cure” worse than the disease.

Jason P. Sheehan
Charlottesville, Virginia

John R. Adler, Jr.
Stanford, California

This is an excellent study from a leading radiosurgery group describing their experiences using radiosurgery for the management of intracranial meningiomas. Although retrospective, it does provide useful information that will help clinicians make decisions regarding when to use radiosurgery to treat meningiomas.

Kondziolka et al. report an overall control rate for patients with benign meningiomas (WHO Grade I) of 93%, but for patients with WHO Grade II and III tumors, the control rates were 50 and 17%, respectively. The overall morbidity rate was noted as 7.7%; however, the median follow-up period for patients with WHO Grade II and III tumors is short. The median follow-up periods are 2 years and 15 months, respectively, and the 5-year actuarial control rate was 40% for Grade II tumors and 15% for Grade III tumors. In contrast, the 15-year actuarial tumor control rate for Grade I meningiomas was noted as 87%. The method of reporting tumor control could overestimate the success rate of radiosurgery, as the cohort may have included asymptomatic patients who could have been followed with imaging for years before treatment was necessary.

I do have some concern regarding using radiosurgery as a “definitive” management for patients in whom there has been no biopsy. It is noted that the authors report “an error of 2.3%” in the diagnosis of benign meningioma. Personally, I very much doubt that radiosurgery replaces standard surgery as a primary treatment option for those tumors that can be relatively easily resected, although I think it is a useful adjuvant for the treatment of residual tumor within the cranial base or cavernous sinus after resection of larger cranial base tumors.

Nevertheless, this article provides very useful information that will help clinicians make their management decisions for each individual patient. This will inevitably be based on the size of the tumor, its location, involvement of critical vascular and neural structures, ease of resectability, presenting clinical features, and the patient’s individual characteristics, including age and wishes.

Andrew H. Kaye
Melbourne, Australia

Over more than a decade, dozens of publications have provided convincing evidence to support the use of radiosurgery in selected patients with meningiomas. However, the paucity of published, long-term studies remains a common criticism of a primary radiosurgical approach to such slow-growing lesions. This fact, and a lingering fear of inducing secondary malignancies with ionizing radiation, has limited the acceptance of radiosurgery for many younger meningioma patients. The latter concern, i.e., the induction of new cancers, was somewhat allayed by the recent publication in Neurosurgery by Rowe et al. (1). However, the significance of the current report is that it begins to fill the major void in long-term follow-up after radiosurgical ablation. Given the challenges in conducting such studies, the authors are to be congratulated. I hope radiosurgery has now been used long enough for us to start anticipating that other radiosurgical centers will soon be reporting similar favorable experiences with meningiomas. If so, the argument for using radiosurgery to manage small meningiomas in all age groups may prove thoroughly compelling.

Over the last two decades, radiosurgery has flourished as a safe and effective option for selected meningiomas. Why then, do clinical studies on this topic continue to provoke controversy? Part of the problem is that contemporary studies (surgical case series are no exception to this) often serve as a referendum on which strategy deserves a designation as definitive or absolute. This logic attempts to impart supremacy to one technique over another, rather than determining the appropriate settings in which a clinical team skilled in all techniques should rationally apply one versus another to best care for patients. Declaring a therapy for meningiomas as “definitive” can obscure the desired goal of selecting patient therapy through a measured analysis of risks and benefits that integrate complementary and often interchangeable management strategies based on specific clinical characteristics.

In this article, Kondziolka et al., who are among the most knowledgeable and experienced clinicians in the radiosurgery field, present a retrospective review of 972 patients with 1045 intracranial meningiomas that were managed with stereotactic radiosurgery during an 18-year period. The series was 70% women, 49% of whom had a previous resection and 5% of whom had previous fractionated radiation therapy. An important observation from this study is the low rate of treatment-related complications and the absence of radiation-induced tumors. Despite the large number of patients treated, the study is limited by its retrospective design incorporating a heterogeneous mixture of patients without stratification of clinical features. Because patients with a wide range of inclusion criteria are analyzed collectively, including patients who decided against other treatments and asymptomatic patients who chose against observation, the implications for clinical decision-making are imprecise. This creates groups of patients that do not share important clinical features, such as location, likelihood of gross total resection, presence of symptoms, progressive disease, and presence of prior therapy, making it difficult for clinicians to benefit from the authors’ extensive experience. Additionally, most patients had a median follow-up of less than 4 years, which is insufficient for determining long-term efficacy for a tumor type that can often have an indolent natural history.

The authors’ most provocative conclusion for clinical practice is that radiosurgery can be considered a primary treatment modality for meningiomas without consideration for location and probability of surgical resection. That there are significant benefits to radiosurgery is no longer debatable, and the authors have historically been leaders in demonstrating this to an often skeptical mass of neurosurgeons, but, as clinical therapies evolve, it is desirable to match appropriate treatment modalities to individual patients and consider complementary treatment strategies rather than embrace a debate over surgery versus radiosurgery (or even conservative management) as the “definitive” treatment for meningiomas in the absence of a carefully defined and unbiased context. A more appropriate conclusion of this study might be that radiosurgery plays an important role in selected patients and may be definitive in many patients. This includes an acknowledgment that many meningioma patients (e.g., those with small right frontal convexity tumors) could expect favorable outcomes from either radiosurgery, surgery, or conservative management and that there is considerable overlap among these target populations. Which management strategy is “definitive” would depend on characteristics specific to the individual patient. Retrospective studies on preselected meningioma patients are not sufficiently rigorous to support conclusions regarding “definitive management” of this diverse and heterogeneous group of patients. We hope that future analyses from the valuable patient database in this study will clarify some of these important concerns.

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