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Long-term Tumor Control of Benign Intracranial Meningiomas After Radiosurgery in a Series of 4565 Patients

BACKGROUND: Radiosurgery is the main alternative to microsurgical resection for benign meningiomas.

OBJECTIVE: To assess the long-term efficacy and safety of radiosurgery for meningiomas with respect to tumor growth and prevention of associated neurological deterioration. Medium- to long-term outcomes have been widely reported, but no large multicenter series with long-term follow-up have been published.

METHODS: From 15 participating centers, we performed a retrospective observational analysis of 4565 consecutive patients harboring 5300 benign meningiomas. All were treated with Gamma Knife radiosurgery at least 5 years before assessment for this study. Clinical and imaging data were retrieved from each center and uniformly entered into a database by 1 author (A.S.).

RESULTS: Median tumor volume was 4.8 cm^3, and median dose to tumor margin was 14 Gy. All tumors with imaging follow-up $<$ 24 months were excluded. Detailed results from 3768 meningiomas (71%) were analyzed. Median imaging follow-up was 63 months. The volume of treated tumors decreased in 2187 lesions (58%), remained unchanged in 1300 lesions (34.5%), and increased in 281 lesions (7.5%), giving a control rate of 92.5%. Only 84 (2.2%) enlarging tumors required further treatment. Five- and 10-year progression-free survival rates were 95.2% and 88.6%, respectively. Tumor control was higher for imaging defined tumors vs grade I meningiomas ($P < .001$), for female vs male patients ($P < .001$), for sporadic vs multiple meningiomas ($P < .001$), and for skull base vs convexity tumors ($P < .001$). Permanent morbidity rate was 6.6% at the last follow-up.

CONCLUSION: Radiosurgery is a safe and effective method for treating benign meningiomas even in the medium to long term.

KEY WORDS: Control rate, Follow-up, Meningiomas, Multicenter study, Radiosurgery

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Complete resection, including dural base and underlying bone, is the usual treatment for benign intracranial meningiomas when achievable. In other cases, radiosurgery (RS) is frequently considered. Although a role for RS in the management of benign meningiomas has been well established over the past decade, the optimal management of these relatively common tumors remains unclear despite a large number of reports.[1]

This report reviews the experience of 15 European Gamma Knife centers using RS to treat these tumors. Information was retrieved from a cohort of patients harboring $>$ 4500 benign meningiomas. The primary end point was to evaluate the effect of RS as assessed by imaging to confirm control of tumor progression and to assess the influence of several variables on outcome. The secondary end point was to confirm treatment safety by establishing clinical neurological stability and complication rates after RS.

ABBREVIATIONS: PFS, progression-free survival; **RS,** radiosurgery; **WHO,** World Health Organization

PATIENTS AND METHODS

Study Design

This study was initiated by the European Gamma Knife Society. The Gamma Knife center in Krefeld,

Germany, was appointed to coordinate this research and to define the study protocol.

Description—Data Retrieval

We first defined a suitable database and pattern for data retrieval, which was then divided into 2 sections. The first section included clinical and neurological status before RS, treatment parameters, and tumor features. The second section included imaging and clinical follow-up over the course of the study. All centers contributed a minimum of 50 meningiomas, the first tumor in each center having been treated before the end of 2000. An agreement was made with all treating physicians that cohort details, diagnostic, treatment, and follow-up protocols and other necessary information would be made accessible to an independent investigator (A.S.) as required.

After the protocol was defined, data were retrieved. To make this process as uniform as possible, all treatment protocols and follow-up material were retrospectively reviewed personally by a single visiting fellow (A.S.). Each center was visited at least once over a period of 18 months; data were drawn from imaging studies, clinical notes, and the local databases in all 15 centers under the supervision of the referring neurosurgeon and with the cooperation of 3 clinical fellows. These data were then unified into a single database and completed in accordance with the defined model.

Each referring physician received a copy of the local database adapted to the model of the mean database in order to monitor in second time the quality of retrieval. The first investigator had free access to clinical and personal data of patients, and all such data were retrieved anonymously. No patient names or other forms of personal identification were entered into the database thus produced. A single unique identification number was attributed to each center, and another unique number was allocated to each individual patient to allow a center-stratified analysis. No member had a copy of the main database, such a copy being generated solely for the purpose of statistical analysis after prior approval of each member.

Data were collected only from patients who had undergone RS $>$ 5 years before this visit. Between May 1987 and November 2003, 4517 patients harboring 5062 meningiomas were treated in these participating centers. To avoid bias in assessment of short-term clinical outcomes, we included at this stage the treatment of another 238 tumors in patients already in the study cohort that had been treated after November 2003. Sixty-nine patients undergoing repeat RS for 71 enlarging tumors were considered to be new cases. Forty-one tumors not considered to be suitable either for surgery debulking or for total microsurgical resection were treated with volume-staged procedures. These were considered 2 separate treatments for distinct tumor portions within a time frame of 6 months. A cohort of 4565 patients harboring exactly 5300 meningiomas was reviewed; these details are shown in Table 1. Anatomical tumor distribution is shown in Table 2. All tumors included were either histologically confirmed as World Health Organization (WHO) grade I or were diagnosed presumptively on the basis of imaging. Radiosurgery was usually performed under local anesthesia supplemented, if necessary, by sedation. The Leksell Gamma Knife (Elekta Instruments AB) and KULA Planning System with computed tomography (CT) imaging was initially used in some centers, later replaced by Leksell Gamma Plan System and magnetic resonance image (MRI) scanning, respectively. Patients treated with pre-CT radiosurgical plans were excluded. Indications for radiosurgical treatment were tumor remnant or recurrence after surgical resection, with maximum major tumor diameter $<$ 3 cm and with acceptable dose delivery to adjacent eloquent structures.

TABLE 1. Characteristics of 4565 Patients Treated With Radiosurgery

Characteristic	
Patient data	
Age at treatment, y[a]	57 ± 13.4
Female sex, n (%)	3404 (74.6)
Male sex, n (%)	1161 (25.4)
Patients with sporadic meningiomas, n (%)	4090 (89.6)
Patients multiple meningiomas, n (%)[b]	415 (9.1)
Patients with neurofibromatosis type 2, n (%)[b]	60 (1.3)
Clinical-neurological picture, n (%)[c]	
Headache	811 (17.7)
Seizures	322 (7.1)
Cranial nerve deficit	2561 (56.1)
Hemiparesis, hypoesthesia	513(11.3)
Imbalance ataxia-vertigo	585 (12.3)
Details of meningiomas radiosurgery	
Volume, cm^3[a,d]	4.8 ± 7.0
Imaging-defined meningiomas, n (%)	2976 (56.2)
Grade I meningiomas, n (%)	2324 (43.8)
Sporadic meningiomas, n (%)[b]	4157 (78.4)
Multiple meningiomas, n (%)[b]	969 (18.2)
Neurofibromatosis type 2 meningiomas, n (%)[b]	174 (0.4)
Maximal dose, Gy[a]	28.0 ± 7.2
Margin dose, Gy[a]	14.0 ± 3.0
Isodose, Gy[a]	50 ± 7.0
Isocenters[a,d]	9 ± 8.0
Dose to optic pathways, Gy[a]	8.0 ± 9.2
Follow-up	
Radiological follow-up, mo[a]	63 ± 32
Clinical follow-up, mo[a]	61 ± 38
Patients lost to follow-up, n (%)	528 (11.5)
Tumors lost to follow-up, n (%)	715 (13.5)
Tumors with follow-up $>$ 5 y, n (%)	1334 (29.1)
Tumors with follow-up $>$ 7.5 y, n (%)	577 (12.6)
Tumors with follow-up $>$ 10 y, n (%)	388 (8.4)

[a]Median (SD).
[b]Mutiple meningiomas were defined as $>$ 1 tumor treated in the same or different session not having recurred within the surgical field. For all patients diagnosed with neurofibromatosis type 2 regardless of tumor count, treatments were analyzed separately.
[c]Number of symptomatic cases do not correspond to the number of patients because some of these had $>$ 1 symptom; 981 patients (21.4%) were asymptomatic.
[d]Volume was available at time of treatment for 4614 tumors and isocenter for 4624 treatments.

Specifically, in patients with intact vision, the marginal dose to any part of the optic apparatus was restricted to 10 Gy.

We defined sporadic as a single meningioma treated in a single patient and multiple as $\geq$ 2 meningiomas, these not being recurrences from within a single surgical field. Within the second group, we then identified and subdivided lesions associated with neurofibromatosis type 2 and those patients with frank meningiomatosis.

Imaging Follow-up

Serial imaging (MRI or CT when MRI was contraindicated) was performed at various times according to center, and results were collated in

TABLE 2. Locations for 5300 Benign Intracranial Meningiomas[a]

Location	n
Orbit	80
Sagittal sinus[b]	80
Parasagittal[b]	157
Anterior cranial fossa[c]	85
Cerebellopontine angle	432
Falx	445
Frontal	42
Convexity	591
Middle cranial fossa[c]	363
Olfactory groove	53
Optic nerve sheath	41
Other	43
Petroclival	468
Posterior cranial fossa[c]	241
Pineal region	26
Cavernous sinus	1272
Intrasellar	80
Sphenoid wing	280
Temporal	83
Tentorium	402
Ventricular	36

[a]Anatomic locations were defined according to the classification proposed by Yasargil (Yasargil MG. *Microneurosurgery*. Stuttgart, Germany: Georg Thieme Verlag, 1996; IVB:134-165.).
[b]Meningiomas close to the sagittal sinus were stratified in those infiltrating the sinus and those without clear infiltration.
[c]Tumor arising from encoded locations, eg, petroclival region, and spreading within the specified intracranial fossa.

the follow-up section of the main database. Qualitative and quantitative evaluations of tumor size were performed on each examination by the local staff and independently reviewed by the first investigator (A.S.), who also compared reported outcomes. Tumor volume on each scan was compared with the tumor volume before RS. If the imaging material was digitalized, a volumetric measurement was performed with dedicated software. When imaging was available only on celluloid film, the comparison was made by measuring and comparing the 3 major diameters. Shrinkage or enlargement was defined as an imaging-assessed change in tumor volume of at least 10% determined (as described above) either by direct volumetric measurement or by calculation based on dimensions.

Neurological Picture and Clinical Follow-up

Before treatment, all patients underwent neurological examination, which was available for 4541 patients. These were standardized according to a uniform classification[2]: 0 = no neurological deficit, 1 = mild or intermittent neurological deficit, 2 = persisting neurological deficit but not affecting performance in daily life, and 3 = permanent/severe neurological deficit affecting performance in daily life. Epileptic seizures were classified as follows: 0 = no seizure activity, 1 = partial seizures, and 2 = generalized seizures. Each epileptic category was subdivided into temporary and permanent subgroups. Clinical and imaging follow-up were performed thereafter.

Any neurological deficit newly reported or reported to be worsening after RS was carefully evaluated and defined as a complication. Complications were then further divided into temporary and permanent subgroups. The latest clinical follow-up is reported separately from the imaging follow-up. In the event of death, date of death was considered to be the date of latest clinical follow-up, and the cause of death was classified as treatment related (treatment), tumor related (meningioma), unrelated (other), or unclear (unknown). Complications are described separately in patients who died of unclear causes. Patients without clinical control were defined as lost to follow-up, and patients without imaging follow-up were defined as lost to imaging follow-up. They are not included in the statistical analysis.

Survey of Patients

All patients had therefore been treated at least 5 years before this retrieval visit, but it does not follow that all tumors had an effective follow-up time frame of $\geq$ 5 years. A survey of patients lost to follow-up was conducted at 5 years in 11 centers by sending a follow-up letter to the patient or referring physician. Patients were asked to undergo further imaging and neurological evaluation at the treating center, and physicians were asked to provide updates based on this imaging and to plan any necessary further imaging accordingly. They were then requested to return such results to the treating center; these results were then subsequently collected by the local fellow and finally reviewed and collated by the first investigator (A.S.).

Statistics

Analysis was performed solely with respect to imaging follow-up, and time to enlargement of tumor was estimated with the Kaplan-Meier method. This time was defined by date of the first scan to show enlargement, rather than by time to effective regrowth. Analysis focused solely on the first tumor treated to avoid any dependency on a potentially variable number of meningiomas treated per patient. All tumors with follow-up $<$ 24 months were excluded. Independent variables were evaluated separately to ascertain their influence on imaging tumor control.

Univariate comparisons between noncontinuous variables (histology, sex, multiple/sporadic tumors) and location (skull-base/convexity) were performed with the log rank test. Univariate analysis for continuous variables (prescription dose, maximum dose, age, volume) was performed by applying the Cox proportional hazard model. Multivariate analysis was performed using stepwise Cox regression. For the purposes of this analysis, we used only those variables that had been demonstrated by the prior univariate analysis to be relevant. Meningiomatosis and neurofibromatosis type 2 cases were analyzed separately and singularly compared with sporadic cases to evaluate a statistically significant difference in outcome with respect to image-assessed tumor control. Convexity tumors and meningiomas in other non–skull base locations were singularly compared with skull base tumors in an attempt to elucidate any statistically significant difference with respect to image-assessed tumor control.

Comparison of tumor volume between location subgroups was performed by use of the Mann-Whitney test. Statistical analyses were performed with the SAS software package (SAS for Windows, version 9.1; SAS Institute Inc, Cary, North Carolina).

RESULTS

Of 4565 patients treated, 528 (11.5%) were lost to follow-up. Detailed results for 4585 tumors (86.5%) were collected in the main database.

Imaging Follow-up

Imaging follow-up ranged from 24 to 233 months, with a total of 817 tumors whose imaging follow-up was < 24 months being excluded. From this cohort, we obtained follow-up for > 5, 7.5, and 10 years in 1334, 577, and 388 tumors, respectively. Median imaging follow-up was 63 months (mean, 70.9 months). According to our data, of 3768 tumors with at least 24 months of follow-up, a total of 2107 have digitally stored images.

We found that 2187 meningiomas (58%) had regressed (reduced in size) and 1300 tumors (34.5%) had remained unchanged, giving a tumor control rate of 92.5%. Overall tumor control is shown in the Figure. Tumor progression occurred in 281 lesions (7.5%) at a median of 48.7 months (mean, 56 months). Forty-one patients harboring 43 tumors underwent further treatment. Conventional radiotherapy or repeat RS was performed in 13 of these patients, and 27 of them underwent surgery. One patient who underwent repeated RS eventually required surgery after further tumor enlargement. The remaining 197 tumors had not required further treatment by the time of last follow-up.

The Kaplan-Meier estimations of progression-free survival (PFS) at 5, 7.5, and 10 years showed control rates of 95.2%, 91.3%, and 88.5%, respectively. We observed PFS rates of 92.7%, 86.4%, and 83.2% for those tumors initially treated with microsurgery vs 96.8%, 95.1%, and 92.7%, respectively, for tumors without histological confirmation. Imaging tumor control was better in female than in male patients ($P < .001$), better for those who had not undergone previous surgery ($P < .001$), poorer for those demonstrating increasing tumor volume ($P = .01$), and better for patients suffering from single as opposed to multiple meningiomas ($P < .001$). Skull base tumors were better controlled than convexity lesions ($P < .001$; Tables 3–5). A statistical difference in tumor control between centers is also observed ($P < .001$). The Mann-Whitney test demonstrated a statistical difference about volume between convexity and skull base tumors (2-sided $P < .001$).

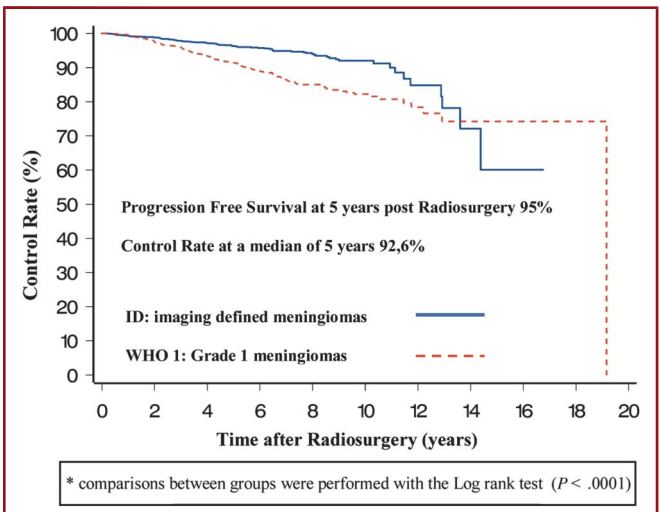

FIGURE. *Kaplan-Meier test showing local imaging tumor control after radiosurgery plotted by tumors without histological confirmation (ID) and histologically confirmed benign meningiomas (World Health Organization [WHO] grade I).*

Neurological Picture and Clinical Follow-up

Descriptive clinical follow-up was obtainable for 3854 patients (84.4%) and ranged from 6 to 233 months. Clinical improvement was reported in 2065 patients (53.5%) at a median follow-up of 61 months (mean, 61.8 months), and complete resolution of symptoms was reported in 865 cases (22.2%). Complications were observed after RS in 497 patients (12.9%), as detailed in Table 6. Morbidity rates were 6.3% (temporary) and 6.6% (permanent). We assessed grade 1 morbidity at 4.7 %, grade 2 morbidity at 6.8%, and grade 3 morbidity at 1.3%. Permanent grade 2 morbidity was 3.6% and permanent grade 3 morbidity was 1.2%. Morbidity for skull base meningiomas (356 of 2101 cases) was 16.9%, including 36 cases (1.7%) in which grade 3 morbidity was permanent. Morbidity for convexity/parasagittal locations was seen in 124 of 832 cases (14.9%), permanent and disabling in 10 cases (1.2%). In particular, symptomatic edema occurred in 39 cases (4.7%). Morbidity for cavernous sinus, sellar, and middle cranial fossa locations was seen in 148 of 1380 cases (10.7%). Among these complications, 62 were in patients who had harbored tumors that had enlarged, 40 of them previously confirmed (after surgery) as WHO grade I. Four patients who developed a complication eventually died: 3 died of edema/swelling after staged RS for large parasagittal meningiomas and 1 died of hydrocephalus/radionecrosis after RS for a posterior cranial fossa meningioma.

Six patients who developed complications at a mean of 14.5 months after RS eventually died of unknown causes at a mean of 54 months, although only 2 had previously developed permanent complications. The remaining 6 died of unrelated causes. Five patients underwent surgery despite good tumor control: 2 for chronic subdural hematoma at another location, 2 for cystic degeneration close to the volume irradiated, and 1 for severe facial pain associated with a petroclival meningioma that persisted after RS. No radiation-induced tumors were seen, but of 8 patients reoperated on for post-RS tumor enlargement, 6 demonstrated atypical histology (WHO grade II) and 2 were frankly malignant (WHO grade III), all having been reported at previous surgery as having WHO grade I lesions.

DISCUSSION

Radiosurgery does not achieve tumor removal, the claimed outcome of a radical microsurgical resection, but it can frequently achieve simple control of tumor volume. The main goal of RS is to control tumors not amenable to complete resection such as those in high-risk locations where postoperative complications might be anticipated or residual or recurrent tumors. Our study describes the largest cohort ever reported in the literature.[1,3]

TABLE 3. Progression-Free Survival Rate at 5, 7.5, and 10 Years After Radiosurgery[a]

Variable	5 Years, %	7.5 Years, %	10 Years, %
ID meningioma	96.8 (95.8-97.6)	95.1 (93.6-96.3)	92.7 (90.3-94.5)
Grade I meningioma	92.7 (91.1-93.9)	86.4 (83.8-88.5)	83.2 (79.9-86.0)
Female	96.3 (95.4-97.0)	93.2 (91.8-94.4)	91.6 (89.1-92.8)
Male	90.3 (87.7-92.3)	83.5 (79.6-86.7)	78.1 (72.4-82.7)
Sporadic meningioma[b]	95.4 (94.5-96.2)	92.7 (91.4-93.9)	89.9 (87.9-91.7)
Multiple meningioma[b]	91.2 (87.3-93.9)	78.4 (71.5-83.9)	76.1 (68.6-82.1)
Neurofibromatosis type 2 meningioma[b]	87.2 (73.2-93.9)	83.2 (67.2-91.8)	77.6 (57.7-89.0)
Skull base meningioma[c]	95.9 (94.9-96.6)	92.4 (90.9-93.7)	90.1 (87.9-91.8)
Convexity meningioma[c]	91.6 (89.1-93.6)	85.9 (81.9-89.1)	81.6 (75.8-86.1)
Other locations of meningioma[c]	90.7 (80.1-95.7)	87.2 (73.5-94.0)	82.0 (63.7-91.6)

[a]Grade 1, World Health Organization grade I; ID, imaging-defined; PFS, progression-free survival. Values in parentheses are 95% confidence limits.
[b]Multiple meningiomas were encoded as 1 (no) or > 1 (yes) meningioma treated. Neurofibromatosis type 2 meningiomas were analyzed separately.
[c]Location groups classified as skull base, convexity, and other intracranial location.

Long-term follow-up is essential for the assessment of the efficacy of RS in this or, for that matter, other situations. We have collated patients treated at least 5 years before the retrieval visit, and we have obtained median imaging follow-up of 63 months, one of the longest follow-up periods reported so far. Nevertheless, this study does have some limitations. It is retrospective and center biased. However, its database is not simply a mass of material drawn from questionnaires sent to the participating centers but instead consists of unified data collated by 1 individual supervised by the local staff according to a defined protocol. All further treatments undertaken for local or out-of-field recurrence have also been included, even after the observation interval. This helps give a clearer picture of the possible biological tissue effects of several procedures and thus potential radiosurgically related morbidity. However, this may bias the local tumor control rate, reported as 92.5%, by "lumping together" all treatments regardless of the number of lesions treated per patient and the observation interval. To adjust for this potential bias, we focused solely on the first tumor irradiated in each patient, in which we report a 5-year PFS rate of 95%, thus confirming this control rate in > 90% of patients. Furthermore, 41 patients underwent volume-staged RS. We decided to consider each treatment separately (2 per tumor) to understand, after recurrence, which treatment had failed, potentially biasing the analysis by a factor of only something less than 1%.

Another potential bias is the time to tumor progression. This was coded from the time of the imaging study that showed progression, rather than time of initial regrowth. However, because the median time to enlargement is reported at 48 months (mean, 56 months), we can state that a recurrence occurs in a shorter time frame than the follow-up period observed. A further point of discussion is provided by the patient population with short imaging follow-up. In accordance with most current literature, we have excluded from statistical analysis all patients/tumors with follow-up < 24 months. However, to keep our report unbiased with respect to cases of early complications after treatment (which might otherwise be missed and therefore be underreported), we have kept these in the descriptive clinical-neurological follow-up. A substantial bias might also be introduced by the use of different planning systems and imaging

TABLE 4. Univariate Analysis of Imaging Tumor Control Defined as Stable or Regressed Size of the Tumor Irradiated

Univariate χ^2 for the Log Rank Test

Variable	χ^2	Probability > χ^2
Previous surgery[a]	35.6102	<.001
Sex	52.4086	<.001
Multiple meningiomas[b]	33.2440	<.001
Location group[c]	27.8084	<.001

Unifactorial Cox Proportional Hazard Model

Variable	Probability > χ^2	Hazard Ratio	95% Confidence Limits
Center	<.001		
Previous surgery[a]	<.001	0.441	0.335-0.582
Age	.38	0.995	0.985-1.006
Sex	<.001	2.564	1.968-3.340
Volume	.013	1.020	1.004-1.036
Prescription dose	.08	1.035	0.996-1.075
Sporadic tumors vs meningiomatosis[b]	<.001	2.332	1.687-3.222
Sporadic tumours vs neurofibromatosis type 2 tumors[b]	.006	2.564	1.310-5.017
Skull base vs convexity[c]	<.001	2.072	1.564-2.744
Skull base vs other locations[c]	0.1181	1.766	0.865-3.606

[a]Previous surgery implies histological confirmation of World Health Organization grade I meningioma.
[b]Multiple meningiomas were coded as 1 (no) or > 1 (yes) meningioma treated. Neurofibromatosis type 2 meningiomas were analyzed separately.
[c]Location groups classified as skull base, convexity, and other intracranial location .

TABLE 5. Multivariate Analysis of Imaging Tumor Control Defined as Stable or Regressed Size of the Tumor Irradiated

Multifactorial Cox Regression			
Variable	Probability $> \chi^2$	Hazard Ratio	95% Confidence Limits
Center	<.001		
Previous surgery[a]	<.001	0.494	0.358-0.682
Sex	<.001	1.965	1.445-2.672
Volume	.02	1.020	1.003-1.037
Sporadic tumors vs meningiomatosis[b]	.007	1.730	1.161-2.577
Sporadic tumors vs neurofibromatosis type 2 tumors[b]	.06	2.130	0.971-4.672
Skull base vs convexity[c]	.001	1.704	1.209-2.401
Skull base vs other locations[c]	.04	1.397	0.643-3.036

[a]Previous surgery implies histological confirmation of World Health Organization grade I meningioma.
[b]Multiple meningiomas were encoded as 1 (no) or > 1 (yes) meningioma treated.
[c]Location groups classified as skull base, convexity, and other intracranial location.

techniques over the years covered by the study. All centers that were treating before 1993 had a CT-based radiosurgical plan. Between 1994 and 1996, Leksell Gamma Plan was gradually introduced, together with MRI planning. In smaller centers, starting in 1998, all tumors were planned with Leksell Gamma Plan and imaged by MRI. Twenty-four patients who had not undergone pretreatment neurological assessment were included because 13 of them died over the years covered by the study. All these patients had imaging follow-up at a median of 46 months.

According to our results, various factors may influence imaging outcome. We found, contrary to other series,[3] that previous surgery is a significant factor with respect to imaging tumor control. A possible reason may be that highly conformal planning is easier for lesions with a morphology that has not been altered by prior surgery, given the postoperative distortions that enhancing scar tissue can introduce. Poorer control in male than female patients has been previously reported.[4] The reason for this is unknown but may relate to hormonal status.[5]

It is still not entirely clear which meningiomas should undergo microsurgery and which should receive RS as the first treatment option. Meningiomas tend to vary greatly in volume, shape, location, and clinical manifestations.[1] A number of reports over the years have proposed RS not only for patients harboring recurrent or residual tumors after microsurgery but also for patients with newly diagnosed tumors without histological confirmation.[1,4,6-16]

Many surgeons have advocated monitoring by serial imaging after subtotal resection rather than offering adjuvant radiotherapy

TABLE 6. Complications After Radiosurgery in 497 Patients[a]

Sign/Symptom	Mild, n	Continuous but not Disabling, n	Continuous and Disabling, n	Temporary, n	Permanent, n
Imbalance, ataxia, dizziness, vertigo	17	12	3	18	14
Vision trouble	8	9	11	5	23
Oculomotor palsy	9	27	12	15	33
Trigeminal symptoms	34	48	5	50	37
Facial palsy	8	4	3	5	10
Hearing loss, tinnitus	5	12	2	8	11
Symptomatic edema	16	48	0	44	20
Seizures[b]	37	21	. . .	40	18
Headache	41	57	7	44	61
Hemiplegia, hemiparesis	2	13	8	6	17
Hemiypoaesthesia	1	1	0	1	1
Other	5	11	0	8	8
Permanent mild morbidity rate, 1.8%					
Permanent continuous (not disabling) morbidity rate, 3.6%					
Permanent continuous (disabling) morbidity rate, 1.2%					

[a]Morbidity rate is calculated from those patients with a detailed neurological examination (3854 patients). Some patients exhibited > 1 sign/symptom.
[b]Epilepsy classification: 0 = no symptoms, 1 = partial seizure, 2 = generalized seizures. Each category was then divided into temporary or permanent subgroups.

or RS. Our results put this "wait and see" policy in a new perspective. Recurrence after subtotal microsurgical resection is not uncommon, and this "wait and see" question should perhaps be reconsidered with respect to why we are waiting. Simpson[17] described meningioma (WHO grade I) recurrence rates with reference to the degree of resection, reported to be 9% after complete resection including dural base, 19% after excision and coagulation of the dural base, 29% after excision without coagulation of the dural base, and 40% after subtotal resection. Condra et al[18] confirmed Simpson's results, publishing outcomes in 262 tumors by comparing local tumor control among 3 treatment subgroups: surgery alone, radiotherapy alone, and surgery combined with radiotherapy. They reported a 70% rate of tumor progression for those tumors partially resected without adjuvant radiotherapy. Pollock et al[19] compared tumor control rates after surgical resection or RS for patients with small/medium intracranial meningiomas, finding no statistically significant difference in the 3- and 7-year actuarial PFS rate between patients with Simpson grade 1 resections (100% and 96%, respectively) and patients who underwent RS (100% and 95%, respectively; $P = .94$). RS provided a higher PFS rate than Simpson grade 2 resection (3- and 7-year PFS rate, 91% and 82%, respectively; $P < .05$) and grade 3 to 4 resections (3- and 7-year PFS rate, 68% and 34%, respectively; $P < .001$). These outcomes have been confirmed in other studies.[20,21]

Kaye et al[1] recently commented that methods of reporting control in radiosurgical series might overestimate success rates because the cohort analyzed may also include patients who could otherwise have been followed up for many years with serial imaging before intervention might have been deemed necessary. On the other hand, the purely incidental diagnosis of meningioma is reported to be unusual, suggesting that the majority of these lesions are presenting and being treated, having produced some form of clinical picture that led to their discovery. Vernooij et al,[22] reporting incidental findings on brain MRI from a review of > 2000 scans, found that in only 18 cases (0.9%) were incidental meningiomas diagnosed. Furthermore, conservative management of intracranial meningiomas has already been analyzed in many studies.[23-29] These report imaging tumor growth in 24% to 76% of tumors, suggesting that active treatment is usually required. To raise the question is to imply its own answer: The "wait and see" policy with serial MRI should be reserved for asymptomatic elderly patients with calcified convexity meningiomas.[3,26,27,29] Radiosurgery is a safe method for managing benign meningiomas, as indicated by the very low complication rate.[18,30] Although no development of a radiation-induced tumor has been observed in this study, some attention should nevertheless be paid to this small risk.[15,31]

We do not advocate RS as being definitive or absolute; the end point for any treatment must be long-term efficacy and safety in the management of benign meningiomas. Each case should be carefully evaluated with respect to risk, outcome, and morbidity/mortality, regardless of the mode of management used. Treatment policy should be determined after both options are considered. As microsurgical procedures and imaging techniques have improved decade by decade, RS has also improved, not only because of this improved imaging but also by virtue of better appreciation of indications and improved planning software. As for microsurgery, RS is to a considerable extent operator dependent, and the individual neurosurgeon's experience in the field of RS should be a consideration. Lower tumor control rates can be demonstrated in the pioneering era and in less experienced groups in more recent times.

CONCLUSION

Radiosurgery is a safe and effective method of managing benign intracranial meningiomas. Analysis of the imaging tumor control data shows better outcomes for skull base location, female sex, and sporadic, imaging-defined (not previously operated) tumors. The low neurological morbidity rate indicates patient safety. Although longer follow-up is always desirable, the short median time to recurrence (<5 years) confirms the validity of our data analysis.

Disclosures

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COMMENTS

In this study, Dr Santacroce and colleagues detail results of a retrospective study for 4565 patients treated with Gamma Knife radiosurgery for 5300 meningiomas. Five- and 10-year progression-free survival rates were 94% and 87.5%, respectively. Permanent morbidity was noted in 6.6%, but another 6.3% suffered temporary complications.

Although the study is not without faults (the retrospective nature, differences in selection criteria and techniques between centers, etc.), it unequivocally confirms the efficacy and safety of Gamma Knife radiosurgery for the treatment of patients with grade I meningiomas. This study and others like it have clearly illustrated the largely beneficial effects of Gamma Knife radiosurgery for meningiomas. Studies have clearly differentiated the tumor controlling effects of radiosurgery from the natural history of slow-growing tumors such as benign meningiomas.

Recent work by Dr Sughrue and colleagues[1] suggesting that the benefits of Simpson grade I vs grade II resections may be negligible, coupled with the validated efficacy of radiosurgery for meningiomas, is resulting in a paradigm shift in neurosurgery. An approach wherein one performs cytoreductive surgery leaving behind small portions of tumor adjacent to critical neurovascular structures, bone, or dura, followed by stereotactic radiosurgery to treat the residual meningioma, is providing patients with very acceptable, if not superior, results. The judicious use of both microsurgery and radiosurgery appears to ensure the best long-term outcomes for many patients with meningiomas.[2]

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1. Sughrue ME, Kane AJ, Shangari G, et al. The relevance of Simpson grade I and II resection in modern neurosurgical treatment of World Health Organization grade I meningiomas. *J Neurosurg*. 2010;113(5):1029-1035.
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The authors report the outcomes of a multicenter retrospective observational outcome analysis of a large group of patients who underwent Gamma Knife radiosurgery for $\geq$ 1 intracranial meningiomas. The amount of data in such a project is seemingly overwhelming. This report provides additional support for the use of radiosurgery for meningiomas. It is valuable for scientific organizations, consortia, and industry to support such studies. Although the level of evidence does not fit the current demands of some journals, relatively few surgical studies provide outcome data in the large volume of patients included in this report. I share the authors' belief that radiosurgery is a low-risk procedure that is highly effective for imaging defined, symptomatic, or growing meningiomas. It is also valuable for recurrent meningiomas or those incompletely removed.

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