

IGKRF

International Gamma Knife Research Foundation

STEREOTACTIC RADIOSURGERY RESEARCH, EDUCATION AND PUBLISHING FOR THE PURPOSE OF IMPROVING PUBLIC HEALTH

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Chairman's Message

Update on IGKRF Activities

It's been a productive year for IGKRF and I am both honored and humbled to become the new Chair of this organization. Ajay Niranjana, our Executive Director has put together an outstanding Newsletter highlighting the organization's accomplishments including our biennial meeting in Philadelphia, and an unprecedented number of publications in 2017. I congratulate and thank our hosts at University of Pennsylvania for a very successful scientific and social agenda. The location and date of IGKRF's next meeting, tentatively slated for 2019, will be forthcoming soon.

Speaking of meetings, some of the IGKRF Executive Committee (which includes Jason Sheehan as Vice-Chair and Veronica Chiang as Secretary/Treasurer) had the opportunity to attend the recent Leksell Gamma Knife Society Meeting in Dubai, United Arab Emirates. This too was an outstanding meeting and IGKRF was highlighted in two presentations which I was asked to give. It was also a bittersweet event as we learned that this would be the last standalone LGKS meeting and that future events would be blended into International Stereotactic Radiosurgery meetings. The end of an Era. Hats off to Danny Leksell for driving this effort for so many years.

As noted above, 2017 was a banner year for IGKRF in terms of publications with a total of 18. The topics proved to be an eclectic mix of pathologies including hemangiopericytomas, hemangiomas, AVMs, pineal region tumors, primary CNS lymphomas, and pituitary adenomas. This record may be hard to duplicate in 2018, but it looks like this should be a productive year as well.

The IGKRF Board will be meeting at the end of this month at the American Association of Neurological Surgeons Meeting in New Orleans. Some provocative topics are on the agenda which could make for some big changes in the IGKRF. Stay tuned.

Gene Barnett, MD

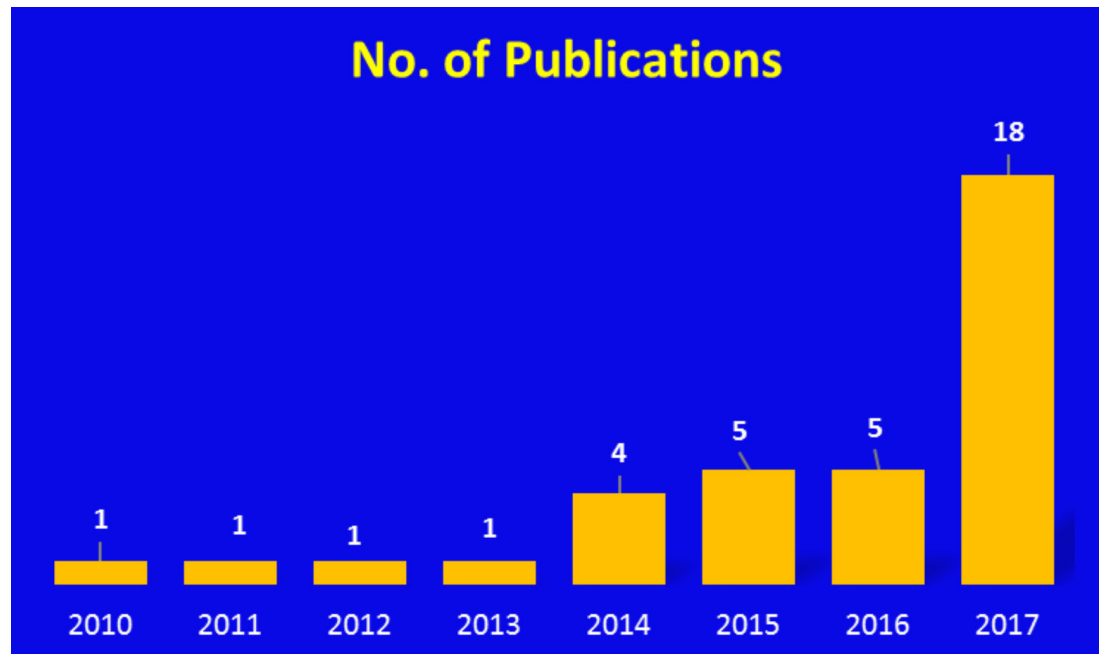
The International Gamma Knife Research Foundation

The International Gamma Knife Research Foundation was organized in 2008 and consists of academic and clinical centers of excellence where brain Stereotactic Radiosurgery is performed using the Leksell Gamma Knife. The primary goal of the IGKRF is to facilitate retrospective and prospective clinical trials and outcomes analysis that evaluate the role of Gamma Knife radiosurgery in a wide spectrum of clinical indications. Because individual centers may evaluate only a small number of patients with rare conditions, performing multi-center trials by pooling of information is critical to evaluate and to improve outcomes. Since its inception more than 35 multicenter retrospective studies have been published by IGKRF members. Eighteen multicenter studies were published in year 2017.

IGKRF's headquarters is currently located at University of Pittsburgh Medical Center (UPMC). Gene Barnett, MD (Chair), Jason Sheehan, MD, PhD (Vice Chair), Veronica Chiang, MD, (Secretary-Treasurer), and L Dade Lunsford (past chair) currently serve as the board members of the executive committee. Ajay Niranjana, MD, MBA serves as the executive director.

Under the direction of the Board, representatives of the member institutions coordinate members' research and publication activities, manage a database of medical information concerning use of the Gamma Knife, and provide communication and administrative support staff. The member organizations of IGKRF are represented by neurological surgeons, radiation oncologists, medical physicists and researchers from leading academic national and international medical facilities.

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IGKRF 2017 Meeting Summary

The IGKRF 2017 Biennial meeting, was held in Philadelphia, June 23rd, 2017. It's Always Sunny in Philadelphia, especially this June 23, 2017 when the International Gamma Knife Research Foundation convened in the Perelman Center for Advanced Medicine at the University of Pennsylvania. Hosted by John Y.K. Lee, MD and Michelle Alonso-Basanta, MD, PhD, this educational event illuminated practitioners from various disciplines and multiple continents, including Americas, Europe and Asia. The focus of the meeting was the "New Era in Biologics and Radiosurgery," and recent developments in immunotherapy were highlighted throughout. The educational event was capped with dinner/reception at the recently relocated Barnes museum, home to one of the largest private collections of Impressionist art, collected by a physician turned pharmaceutical businessman in the 1900s.



Attendees from Philadelphia
2017 meeting

IGKRF Retrospective Studies Published in 2017

1. Stereotactic radiosurgery for intracranial hemangiopericytomas: a multicenter study

JNS

CLINICAL ARTICLE

J Neurosurg 126:744–754, 2017

Stereotactic radiosurgery for intracranial hemangiopericytomas: a multicenter study

Or Cohen-Inbar, MD, PhD,¹ Cheng-Chia Lee, MD,² Seyed H. Mousavi, MD,³ Hideyuki Kano, MD, PhD,³ David Mathieu, MD,⁴ Antonio Meola, MD,³ Peter Nakaji, MD,⁵ Norissa Honea, PhD,⁵ Matthew Johnson, MD,⁶ Mahmoud Abbassy, MD,⁷ Alireza M. Mohammadi, MD,⁷ Danilo Silva, MD,⁷ Huai-Che Yang, MD,² Inga Grills, MD,⁶ Douglas Kondziolka, MD, MSc,⁸ Gene H. Barnett, MD,⁸ L. Dade Lunsford, MD,³ and Jason Sheehan, MD, PhD¹

Objective: Hemangiopericytomas (HPCs) are rare tumors widely recognized for their aggressive clinical behavior, high recurrence rates, and distant and extracranial metastases even after a gross-total resection. The authors report a large multicenter study, through the International Gamma Knife Research Foundation (IGKRF), reviewing management and outcome following stereotactic radiosurgery (SRS) for recurrent or newly discovered HPCs.

Methods: Eight centers participating in the IGKRF participated in this study. A total of 90 patients harboring 133 tumors were identified. Patients were included if they had a histologically diagnosed HPC managed with SRS during the period 1988–2014 and had a minimum of 6 months' clinical and radiological follow-up. A de-identified database was created. The patients' median age was 48.5 years (range 13–80 years). Prior treatments included embolization (n = 8), chemotherapy (n = 2), and fractionated radiotherapy (n = 34). The median tumor volume at the time of SRS was 4.9 cm³ (range 0.2–42.4 cm³). WHO Grade II (typical) HPCs formed 78.9% of the cohort (n = 71). The median margin and maximum doses delivered were 15 Gy (range 2.8–24 Gy) and 32 Gy (range 8–51 Gy), respectively. The median clinical and radiographic follow-up periods were 59 months (range 6–190 months) and 59 months (range 6–183 months), respectively. Prognostic variables associated with local tumor control and post-SRS survival were evaluated using Cox univariate and multivariate analysis. Actuarial survival after SRS was analyzed using the Kaplan-Meier method.

Results: Imaging studies performed at last follow-up demonstrated local tumor control in 55% of tumors and 62.2% of patients. New remote intracranial tumors were found in 27.8% of patients, and 24.4% of patients developed extracranial metastases. Adverse radiation effects were noted in 6.7% of patients. During the study period, 32.2% of the patients (n = 29) died. The actuarial overall survival was 91.5%, 82.1%, 73.9%, 56.7%, and 53.7% at 2, 4, 6, 8, and 10 years, respectively, after initial SRS. Local progression-free survival (PFS) was 81.7%, 66.3%, 54.5%, 37.2%, and 25.5% at 2, 4, 6, 8, and 10 years, respectively, after initial SRS. In our cohort, 32 patients underwent 48 repeat SRS procedures for 76 lesions. Review of these 76 treated tumors showed that 17 presented as an in-field recurrence and 59 were defined as an out-of-field recurrence. Margin dose greater than 16 Gy (p = 0.037) and tumor grade (p = 0.006) were shown to influence PFS. The development of extracranial metastases was shown to influence overall survival (p = 0.029) in terms of PFS; repeat (multiple) SRS showed additional benefit.

Conclusions: SRS provides a reasonable rate of local tumor control and a low risk of adverse effects. It also leads to neurological stability or improvement in the majority of patients. Long-term close clinical and imaging follow-up is necessary due to the high probability of local recurrence and distant metastases. Repeat SRS is often effective for treating new or recurrent HPCs.

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2. Gamma Knife radiosurgery for hemangioma of the cavernous sinus

JNS

CLINICAL ARTICLE

J Neurosurg 126:1498–1505, 2017

Gamma Knife radiosurgery for hemangioma of the cavernous sinus

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Objective: Cavernous sinus hemangiomas (CSHs) are rare vascular tumors. A direct microsurgical approach usually results in massive hemorrhage and incomplete tumor resection. Although stereotactic radiosurgery (SRS) has emerged as a therapeutic alternative to microsurgery, outcome studies are few. Authors of the present study evaluated the role of SRS for CSH.

Methods: An international multicenter study was conducted to review outcome data in 31 patients with CSH. Eleven patients had initial microsurgery before SRS, and the other 20 patients (64.5%) underwent Gamma Knife SRS as the primary management for their CSH. Median age at the time of radiosurgery was 47 years, and 77.4% of patients had cranial nerve dysfunction before SRS. Patients received a median tumor margin dose of 12.6 Gy (range 12–19 Gy) at a median isodose of 55%.

Results: Tumor regression was confirmed by imaging in all 31 patients, and all patients had greater than 50% reduction in tumor volume at 6 months post-SRS. No patient had delayed tumor growth, new cranial neuropathy, visual function deterioration, adverse radiation effects, or hypopituitarism after SRS. Twenty-four patients had presented with cranial nerve disorders before SRS, and 6 (25%) of them had gradual improvement. Four (66.7%) of the 6 patients with orbital symptoms had symptomatic relief at the last follow-up.

Conclusions: Stereotactic radiosurgery was effective in reducing the volume of CSH and attaining long-term tumor control in all patients at a median of 40 months. The authors' experience suggests that SRS is a reasonable primary and adjuvant treatment modality for patients in whom a CSH is diagnosed.

3. International multicenter cohort study of pediatric brain arteriovenous malformations. Part 1: Predictors of hemorrhagic presentation

JNS PEDIATRICS

CLINICAL ARTICLE

J Neurosurg Pediatr 19:127–135, 2017



International multicenter cohort study of pediatric brain arteriovenous malformations. Part 1: Predictors of hemorrhagic presentation

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Inga S. Grills, MD,⁷ Danilo Silva, MD,⁸ Mahmoud Abbassy, MD,⁸ Symeon Missios, MD,⁸
Douglas Kondziolka, MD,⁵ Gene H. Barnett, MD,⁸ L. Dade Lunsford, MD,³ and
Jason P. Sheehan, MD, PhD¹

Objective: Brain arteriovenous malformations (AVMs) are the most common cause of spontaneous intracranial hemorrhage in pediatric patients (age < 18 years). Since the cumulative lifetime risk

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of AVM hemorrhage is considerable in children, an improved understanding of the risk factors influencing hemorrhagic presentation may aid in the management of pediatric AVMs. The aims of this first of a two-part multicenter, retrospective cohort study are to evaluate the incidence and determine the predictors of hemorrhagic presentation in pediatric AVM patients.

Methods: The authors analyzed pooled AVM radiosurgery data from 7 institutions participating in the International Gamma Knife Research Foundation (IGKRF). Patients younger than 18 years at the time of radiosurgery and who had at least 12 months of follow-up were included in the study cohort. Patient and AVM characteristics were compared between unruptured and ruptured pediatric AVMs.

Results: A total of 357 pediatric patients were eligible for analysis, including 112 patients in the unruptured and 245 patients in the ruptured AVM cohorts (69% incidence of hemorrhagic presentation). The annual hemorrhage rate prior to radiosurgery was 6.3%. Hemorrhagic presentation was significantly more common in deep locations (basal ganglia, thalamus, and brainstem) than in cortical locations (frontal, temporal, parietal, and occipital lobes) (76% vs 62%, $p = 0.006$). Among the factors found to be significantly associated with hemorrhagic presentation in the multivariate logistic regression analysis, deep venous drainage (OR 3.2, $p < 0.001$) was the strongest independent predictor, followed by female sex (OR 1.7, $p = 0.042$) and smaller AVM volume (OR 1.1, $p < 0.001$).

Conclusions: Unruptured and ruptured pediatric AVMs have significantly different patient and nidus features. Pediatric AVM patients who possess 1 or more of these high-risk features may be candidates for relatively more aggressive management strategies.

4. International multicenter cohort study of pediatric brain arteriovenous malformations. Part 2: Outcomes after stereotactic radiosurgery

JNS PEDIATRICS

CLINICAL ARTICLE

J Neurosurg Pediatr 19:136–148, 2017

International multicenter cohort study of pediatric brain arteriovenous malformations. Part 2: Outcomes after stereotactic radiosurgery

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Objective: Pediatric patients (age < 18 years) harboring brain arteriovenous malformations (AVMs) are burdened with a considerably higher cumulative lifetime risk of hemorrhage than adults. Additionally, the pediatric population was excluded from recent prospective comparisons of intervention versus conservative management for unruptured AVMs. The aims of this multicenter, retrospective cohort study are to analyze the outcomes after stereotactic radiosurgery for unruptured and ruptured pediatric AVMs.

Methods: We analyzed and pooled AVM radiosurgery data from 7 participating in the International Gamma Knife Research Foundation. Patients younger than 18 years of age who had at least 12 months of follow-up were included in the study cohort. Favorable outcome was defined as AVM obliteration, no post-radiosurgical hemorrhage, and no permanently symptomatic radiation-induced changes (RIC). The post-radiosurgery outcomes of unruptured versus ruptured pediatric AVMs were compared, and statistical analyses were performed to identify predictive factors.

Results: The overall pediatric AVM cohort comprised 357 patients with a mean age of 12.6 years (range 2.8–17.9 years). AVMs were previously treated with embolization, resection, and fractionated external beam radiation therapy in 22%, 6%, and 13% of patients, respectively. The mean nidus volume was 3.5 cm³, 77% of AVMs were located in eloquent brain areas, and the Spetzler-Martin grade was III or

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higher in 59%. The mean radiosurgical margin dose was 21 Gy (range 5–35 Gy), and the mean follow-up was 92 months (range 12–266 months). AVM obliteration was achieved in 63%. During a cumulative latency period of 2748 years, the annual post-radiosurgery hemorrhage rate was 1.4%. Symptomatic and permanent radiation-induced changes occurred in 8% and 3%, respectively. Favorable outcome was achieved in 59%. In the multivariate logistic regression analysis, the absence of prior AVM embolization ($p = 0.001$) and higher margin dose ($p < 0.001$) were found to be independent predictors of a favorable outcome. The rates of favorable outcome for patients treated with a margin dose ≥ 22 Gy vs < 22 Gy were 78% (110/141 patients) and 47% (101/216 patients), respectively. A margin dose ≥ 22 Gy yielded a significantly higher probability of a favorable outcome ($p < 0.001$). The unruptured and ruptured pediatric AVM cohorts included 112 and 245 patients, respectively. Ruptured AVMs had significantly higher rates of obliteration (68% vs 53%, $p = 0.005$) and favorable outcome (63% vs 51%, $p = 0.033$), with a trend toward a higher incidence of post-radiosurgery hemorrhage (10% vs 4%, $p = 0.07$). The annual post-radiosurgery hemorrhage rates were 0.8% for unruptured and 1.6% for ruptured AVMs.

Conclusion: Radiosurgery is a reasonable treatment option for pediatric AVMs. Obliteration and favorable outcomes are achieved in the majority of patients. The annual rate of latency period hemorrhage after radiosurgery for both ruptured and unruptured pediatric AVM patients conveys a significant risk until the nidus is obliterated.

5. Stereotactic radiosurgery for cerebellar arteriovenous malformations: an international multicenter study

JNS

CLINICAL ARTICLE
J Neurosurg 127:512–521, 2017

Stereotactic radiosurgery for cerebellar arteriovenous malformations: an international multicenter study

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 Symeon Missios, MD,⁷ John Y. K. Lee, MD,⁸ Gene H. Barnett, MD, MBA,⁷ Douglas Kondziolka, MD,³
 L. Dade Lunsford, MD,² and Jason P. Sheehan, MD, PhD¹

Objective: Cerebellar arteriovenous malformations (AVMs) represent the majority of infratentorial AVMs and frequently have a hemorrhagic presentation. In this multicenter study, the authors review outcomes of cerebellar AVMs after stereotactic radiosurgery (SRS).

Methods: Eight medical centers contributed data from 162 patients with cerebellar AVMs managed with SRS. Of these patients, 65% presented with hemorrhage. The median maximal nidus diameter was 2 cm. Favorable outcome was defined as AVM obliteration and no posttreatment hemorrhage or permanent radiation-induced complications (RICs). Patients were followed clinically and radiographically, with a median follow-up of 60 months (range 7–325 months).

Results: The overall actuarial rates of obliteration at 3, 5, 7, and 10 years were 38.3%, 74.2%, 81.4%, and 86.1%, respectively, after single-session SRS. Obliteration and a favorable outcome were more likely to be achieved in patients treated with a margin dose greater than 18 Gy ($p < 0.001$ for both), demonstrating significantly better rates (83.3% and 79%, respectively). The rate of latency preobliteration hemorrhage was 0.85%/year. Symptomatic post-SRS RICs developed in 4.5% of patients ($n = 7$). Predictors of a favorable outcome were a smaller nidus ($p = 0.0001$), no pre-SRS embolization ($p = 0.003$), no prior hemorrhage ($p = 0.0001$), a higher margin dose ($p = 0.0001$), and a higher maximal dose ($p = 0.009$). The Spetzler-Martin grade was not found to be predictive of outcome. The Virginia Radiosurgery AVM Scale score ($p = 0.0001$) and the Radiosurgery-Based AVM Scale score ($p = 0.0001$) were predictive of a favorable outcome.

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Conclusions: SRS results in successful obliteration and a favorable outcome in the majority of patients with cerebellar AVMs. Most patients will require a nidus dose of higher than 18 Gy to achieve these goals. Radiosurgical and not microsurgical scales were predictive of clinical outcome after SRS.

6. Stereotactic radiosurgery for Spetzler-Martin Grade III arteriovenous malformations: an international multicenter study.

JNS

CLINICAL ARTICLE
J Neurosurg 126:859–871, 2017

Stereotactic radiosurgery for Spetzler-Martin Grade III arteriovenous malformations: an international multicenter study

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Objective: Because of the angioarchitectural diversity of Spetzler-Martin (SM) Grade III arteriovenous malformations (AVMs), the management of these lesions is incompletely defined. The aims of this multicenter, retrospective cohort study were to evaluate the outcomes after stereotactic radiosurgery (SRS) for SM Grade III AVMs and to determine the factors predicting these outcomes.

Methods: The authors analyzed and pooled data from patients with SM Grade III AVMs treated with SRS at 8 institutions participating in the International Gamma Knife Research Foundation. Patients with these AVMs and a minimum follow-up length of 12 months were included in the study cohort. An optimal outcome was defined as AVM obliteration, no post-SRS hemorrhage, and no permanently symptomatic radiation-induced changes (RICs). Data were analyzed by univariate and multivariate regression analyses.

Results: The SM Grade III AVM cohort comprised 891 patients with a mean age of 34 years at the time of SRS. The mean nidus volume, radiosurgical margin dose, and follow-up length were 4.5 cm³, 20 Gy, and 89 months, respectively. The actuarial obliteration rates at 5 and 10 years were 63% and 78%, respectively. The annual postradiosurgery hemorrhage rate was 1.2%. Symptomatic and permanent RICs were observed in 11% and 4% of the patients, respectively. Optimal outcome was achieved in 56% of the patients and was significantly more frequent in cases of unruptured AVMs (OR 2.3, $p < 0.001$). The lack of a previous hemorrhage ($p = 0.037$), absence of previous AVM embolization ($p = 0.002$), smaller nidus volume ($p = 0.014$), absence of AVM-associated arterial aneurysms ($p = 0.023$), and higher margin dose ($p < 0.001$) were statistically significant independent predictors of optimal outcome in a multivariate analysis.

Conclusions: Stereotactic radiosurgery provided better outcomes for patients with small, unruptured SM Grade III AVMs than for large or ruptured SM Grade III nidi. A prospective trial or registry that facilitates a comparison of SRS with conservative AVM management might further clarify the authors' observations for these often high-risk AVMs.

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7. Radiosurgery for Cerebral Arteriovenous Malformations in A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA)-Eligible Patients.

Radiosurgery for Cerebral Arteriovenous Malformations in A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA)-Eligible Patients A Multicenter Study

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Background and Purpose: The benefit of intervention for patients with unruptured cerebral arteriovenous malformations (AVMs) was challenged by results demonstrating superior clinical outcomes with conservative management from A Randomized Trial of Unruptured Brain AVMs. The aim of this multicenter, retrospective cohort study is to analyze the outcomes of stereotactic radiosurgery for ARUBA-eligible patients.

Methods: We combined AVM radiosurgery outcome data from 7 institutions participating in the International Gamma Knife Research Foundation. Patients with ≥ 12 months of follow-up were screened for ARUBA eligibility criteria. Favorable outcome was defined as AVM obliteration, no postradiosurgery hemorrhage, and no permanently symptomatic radiation-induced changes. Adverse neurological outcome was defined as any new or worsening neurological symptoms or death.

Results: The ARUBA-eligible cohort comprised 509 patients (mean age, 40 years). The Spetzler–Martin grade was I to II in 46% and III to IV in 54%. The mean radiosurgical margin dose was 22 Gy and follow-up was 86 months. AVM obliteration was achieved in 75%. The postradiosurgery hemorrhage rate during the latency period was 0.9% per year. Symptomatic and permanent radiation-induced changes occurred in 11% and 3%, respectively. The rates of favorable outcome, adverse neurological outcome, permanent neurological morbidity, and mortality were 70%, 13%, 5%, and 4%, respectively.

Conclusions: Radiosurgery may provide durable clinical benefit in some ARUBA-eligible patients. On the basis of the natural history of untreated, unruptured AVMs in the medical arm of ARUBA, we estimate that a follow-up duration of 15 to 20 years is necessary to realize a potential benefit of radiosurgical intervention for conservative management in unruptured patients with AVM.

8. Stereotactic Radiosurgery for Brainstem Arteriovenous Malformations: A Multicenter Study

RESEARCH—HUMAN—CLINICAL STUDIES

Stereotactic Radiosurgery for Brainstem Arteriovenous Malformations: A Multicenter Study

BACKGROUND: The management of brainstem arteriovenous malformations (bAVMs) is a formidable challenge. bAVMs harbor higher morbidity and mortality compared to other locations.

Background: The management of brainstem arteriovenous malformations (bAVMs) is a formidable challenge. bAVMs harbor higher morbidity and mortality compared to other locations.

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Objective: To review the outcomes following stereotactic radiosurgery (SRS) of bAVMs in a multicenter study.

Methods: Six medical centers contributed data from 205 patients through the International Gamma Knife Research Foundation. Median age was 32 yr (6-81). Median nidus volume was 1.4 mL (0.1-69 mL). Favorable outcome (FO) was defined as AVM obliteration and no post-treatment hemorrhage or permanent symptomatic radiation-induced complications.

Results: Overall obliteration was reported in 65.4% (n = 134) at a mean follow-up of 69 mo. Obliteration was angiographically proven in 53.2% (n = 109) and on MRA in 12.2% (n = 25). Actuarial rate of obliteration at 2, 3, 5, 7, and 10 yr after SRS was 24.5%, 43.3%, 62.3%, 73%, and 81.8% respectively. Patients treated with a margin dose >20 Gy were more likely to achieve obliteration (P = .001). Obliteration occurred earlier in patients who received a higher prescribed margin dose (P = .05) and maximum dose (P = .041). Post-SRS hemorrhage occurred in 8.8% (n = 18). Annual postgamma knife latency period hemorrhage was 1.5%. Radiation-induced complications were radiologically evident in 35.6% (n = 73), symptomatic in 14.6% (n = 30), and permanent in 14.6% (n = 30, which included long-tract signs and new cranial nerve deficits). FO was achieved in 64.4% (n = 132). Predictors of an FO were a higher Virginia radiosurgery AVM scale score (P = .003), prior hemorrhage (P = .045), and a lower prescribed maximum dose (P = .006).

Conclusion: SRS for bAVMs results in obliteration and avoids permanent complications in the majority of patients.

9. Effect of treatment period on outcomes after stereotactic radiosurgery for brain arteriovenous malformations: an international multicenter study

JNS

CLINICAL ARTICLE

Effect of treatment period on outcomes after stereotactic radiosurgery for brain arteriovenous malformations: an international multicenter study

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Objective: The role of and technique for stereotactic radiosurgery (SRS) in the management of arteriovenous malformations (AVMs) have evolved over the past four decades. The aim of this multicenter, retrospective cohort study was to compare the SRS outcomes of AVMs treated during different time periods.

Methods: The authors selected patients with AVMs who underwent single-session SRS at 8 different centers from 1988 to 2014 with follow-up ≥ 6 months. The SRS eras were categorized as early (1988–2000) or modern (2001–2014). Statistical analyses were performed to compare the baseline characteristics and outcomes of the early versus modern SRS eras. Favorable outcome was defined as AVM obliteration, no post-SRS hemorrhage, and no permanently symptomatic radiation-induced changes (RICs).

Results: The study cohort comprised 2248 patients with AVMs, including 1584 in the early and 664 in the modern SRS eras. AVMs in the early SRS era were significantly smaller ($p < 0.001$ for maximum diameter and volume), and they were treated with a significantly higher radiosurgical margin dose ($p < 0.001$). The obliteration rate was significantly higher in the early SRS era (65% vs 51%, $p < 0.001$), and earlier SRS treatment period was an independent predictor of obliteration in the multivariate analysis ($p < 0.001$). The rates of post-SRS hemorrhage and radiological, symptomatic, and permanent RICs were not significantly different between the two groups. Favorable outcome was achieved in a significantly higher proportion of patients in the early SRS era (61% vs 45%, $p < 0.001$), but the earlier SRS era was not statistically significant in the multivariate analysis ($p = 0.470$) with favorable outcome.

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Conclusions: Despite considerable advances in SRS technology, refinement of AVM selection, and contemporary multimodality AVM treatment, the study failed to observe substantial improvements in SRS favorable outcomes or obliteration for patients with AVMs over time. Differences in baseline AVM characteristics and SRS treatment parameters may partially account for the significantly lower obliteration rates in the modern SRS era. However, improvements in patient selection and dose planning are necessary to optimize the utility of SRS in the contemporary management of AVMs.

10. Stereotactic radiosurgery for Spetzler-Martin Grade IV and V arteriovenous malformations: an international multicenter study

JNS

CLINICAL ARTICLE

Stereotactic radiosurgery for Spetzler-Martin Grade IV and V arteriovenous malformations: an international multicenter study

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Objective: Due to the complexity of Spetzler-Martin (SM) Grade IV–V arteriovenous malformations (AVMs), the management of these lesions remains controversial. The aims of this multicenter, retrospective cohort study were to evaluate the outcomes after single-session stereotactic radiosurgery (SRS) for SM Grade IV–V AVMs and determine predictive factors.

Methods: The authors retrospectively pooled data from 233 patients (mean age 33 years) with SM Grade IV (94.4%) or V AVMs (5.6%) treated with single-session SRS at 8 participating centers in the International Gamma Knife Research Foundation. Pre-SRS embolization was performed in 71 AVMs (30.5%). The mean nidus volume, SRS margin dose, and follow-up duration were 9.7 cm³, 17.3 Gy, and 84.5 months, respectively. Statistical analyses were performed to identify factors associated with post-SRS outcomes.

Results: At a mean follow-up interval of 84.5 months, favorable outcome was defined as AVM obliteration, no post-SRS hemorrhage, and no permanently symptomatic radiation-induced changes (RIC) and was achieved in 26.2% of patients. The actuarial obliteration rates at 3, 7, 10, and 12 years were 15%, 34%, 37%, and 42%, respectively. The annual post-SRS hemorrhage rate was 3.0%. Symptomatic and permanent RIC occurred in 10.7% and 4% of the patients, respectively. Only larger AVM diameter ($p = 0.04$) was found to be an independent predictor of unfavorable outcome in the multivariate logistic regression analysis. The rate of favorable outcome was significantly lower for unruptured SM Grade IV–V AVMs compared with ruptured ones ($p = 0.042$). Prior embolization was a negative independent predictor of AVM obliteration ($p = 0.024$) and radiologically evident RIC ($p = 0.05$) in the respective multivariate analyses.

Conclusions: In this multi-institutional study, single-session SRS had limited efficacy in the management of SM Grade IV–V AVMs. Favorable outcome was only achieved in a minority of unruptured SM Grade IV–V AVMs, which supports less frequent utilization of SRS for the management of these lesions. A volume-staged SRS approach for large AVMs represents an alternative approach for high-grade AVMs, but it requires further investigation.

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11. Radiosurgery for Unruptured Brain Arteriovenous Malformations: An International Multicenter Retrospective Cohort Study

RESEARCH—HUMAN—CLINICAL STUDIES

Radiosurgery for Unruptured Brain Arteriovenous Malformations: An International Multicenter Retrospective Cohort Study

BACKGROUND: The role of intervention in the management of unruptured brain arteriovenous malformations (AVM) is controversial.

Background: The role of intervention in the management of unruptured brain arteriovenous malformations (AVM) is controversial.

Objective: To analyze in a multicenter, retrospective cohort study, the outcomes following radiosurgery for unruptured AVMs and determine predictive factors.

Methods: We evaluated and pooled AVM radiosurgery data from 8 institutions participating in the International Gamma Knife Research Foundation. Patients with unruptured AVMs and ≥ 12 mo of follow-up were included in the study cohort. Favorable outcome was defined as AVM obliteration, no postradiosurgical hemorrhage, and no permanently symptomatic radiation-induced changes.

Results: The unruptured AVM cohort comprised 938 patients with a median age of 35 yr. The median nidus volume was 2.4 cm³, 71% of AVMs were located in eloquent brain areas, and the Spetzler-Martin grade was III or higher in 57%. The median radiosurgical margin dose was 21 Gy and follow-up was 71 mo. AVM obliteration was achieved in 65%. The annual postradiosurgery hemorrhage rate was 1.4%. Symptomatic and permanent radiation-induced changes occurred in 9% and 3%, respectively. Favorable outcome was achieved in 61%. In the multivariate logistic regression analysis, smaller AVM maximum diameter ($P = .001$), the absence of AVM-associated arterial aneurysms ($P = .001$), and higher margin dose ($P = .002$) were found to be independent predictors of a favorable outcome. A margin dose ≥ 20 Gy yielded a significantly higher rate of favorable outcome (70% vs 36%; $P < .001$).

Conclusion: Radiosurgery affords an acceptable risk to benefit profile for patients harboring unruptured AVMs. These findings justify further prospective studies comparing radiosurgical intervention to conservative management for unruptured AVMs.

12. Histology-Stratified Tumor Control and Patient Survival After Stereotactic Radiosurgery for Pineal Region Tumors: A Report From the International Gamma Knife Research Foundation

ORIGINAL ARTICLE



Histology-Stratified Tumor Control and Patient Survival After Stereotactic Radiosurgery for Pineal Region Tumors: A Report From the International Gamma Knife Research Foundation

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Background: Pineal region tumors represent a rare and histologically diverse group of lesions. Few studies are available to guide management and the outcomes after stereotactic radiosurgery (SRS).

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Methods: Patients who underwent SRS for a pineal region tumor and for whom at least 6 months of imaging follow-up was available were retrospectively assessed in 5 centers. Data were collected from the medical record and histology level analyses were performed, including actuarial tumor control and survival analyses.

Results: A total of 70 patients were treated between 1989 and 2014 with a median follow-up of 47 months. Diagnoses were pineocytoma (37%), pineoblastoma (19%), pineal parenchymal tumor of intermediate differentiation (10%), papillary tumor of the pineal region (9%), germinoma (7%), teratoma (3%), embryonal carcinoma (1%), and unknown (14%). Median prescription dose was 15 Gy at the 50% isodose line. Actuarial local control and survival rates were 81% and 76% at 20 years for pineocytoma, 50% and 56% at 5 years for pineal parenchymal tumor of intermediate differentiation, 27% and 48% at 5 years for pineoblastoma, 33% and 100% at 5 years for papillary tumor of the pineal region, 80% and 80% at 20 years for germinoma, and 61% and 67% at 5 years for tumors of unknown histology. New focal neurological deficit, Parinaud syndrome, and hydrocephalus occurred in 9%, 7%, and 3% of cases, respectively.

Conclusions: SRS is a safe modality for the management of pineal region tumors. Its specific role is highly dependent on tumor histology. As such, all efforts should be made to obtain a reliable histologic diagnosis.

13. Relapsed or refractory primary central nervous system lymphoma radiosurgery: report of the international gamma knife research foundation.

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CLINICAL INVESTIGATION

Relapsed or refractory primary central nervous system lymphoma radiosurgery: Report of the International Gamma Knife Research Foundation

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Purpose/Objectives: To report a multi-institutional experience of patients treated with stereotactic radiosurgery (SRS) as part of their treatment course in the management of primary central nervous system lymphoma (PCNSL).

Materials/Methods: We identified 20 patients with PCNSL who underwent SRS treatment for either recurrence or progression of disease from 1995-2014. Patient characteristics, treatment outcomes, and toxicity information were obtained by database and chart review.

Results: Seventeen patients (85%) presented with RPA Class II PCNSL. The median age of this group was 63 years (range, 43-84 years), initially treated with a median of 7 cycles of methotrexate based chemotherapy (range, 3-26 cycles). Six received additional treatment with whole brain radiation (WBRT) to a median dose of 45 Gy (range, 24-50.4 Gy). Thirteen presented with recurrent PCNSL, and seven presented with progression of their initial disease. Twenty patients underwent 22 courses of salvage SRS treatment. Median tumor volume was 4.1 cm³ (range, 0.3-26.2 cm³), and median margin SRS dose was 15 Gy (range, 8-20 Gy). Median follow-up from the time of salvage SRS treatment was 8.6 months (range, 0.4-141.0 months). Following salvage SRS treatment, seventeen patients presented with treatment response (9 complete, 9 partial), including one who experienced partial and complete response to two lesions. Six developed progression of their disease following salvage SRS treatment, with a median time to progression of 10 months (range, 5.5-38.3 months). Toxicity of treatment with SRS was low, with three developing radiation treatment effect requiring no intervention.

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Conclusions: Although methotrexate-based chemotherapy with or without WBRT is the first-line management option for patients with PCNSL, use of SRS as a salvage therapy option was safe and effective in this multi-institutional study. SRS may be an alternative salvage therapy option in properly selected patients with recurrent or progressive PCNSL.

14. Prognostic significance of corticotroph staining in radiosurgery for non-functioning pituitary adenomas: a multicenter study

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CLINICAL STUDY

Prognostic significance of corticotroph staining in radiosurgery for non-functioning pituitary adenomas: a multicenter study

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Silent corticotroph staining pituitary adenoma (SCA) represents an uncommon subset of Non-Functioning adenomas (NFAs), hypothesized to be more locally aggressive. In this retrospective multicenter study, we investigate the safety and effectiveness of Stereotactic Radiosurgery (SRS) in patients with SCA compared with other non-SCA NFA's. Eight centers participating in the International Gamma-Knife Research Foundation (IGKRF) contributed to this study. Outcomes of 50 patients with confirmed SCAs and 307 patients with confirmed non-SCA NFA's treated with SRS were evaluated. Groups were matched. SCA was characterized by a lack of clinical evidence of Cushing disease, yet with positive immunostaining for corticotroph. Median age was 55.2 years (13.7–87). All patients underwent at least one trans-sphenoidal tumor resection prior to SRS. SRS parameters were comparable as well. Median follow-up 40 months (6–163). Overall tumor control rate (TCR) 91.2% (n = 280). In the SCA group, TCR were 82% (n = 41) versus 94.1% (n = 289) for the control-NFA (p = 0.0065). The SCA group showed a significantly higher incidence of new post-SRS visual deficit (p < 0.0001) assigned to tumor progression and growth, and post-SRS weakness and fatigue (p < 0.0001). In univariate and multivariate analysis, only the status of silent corticotroph staining (p = 0.005, p = 0.009 respectively) and margin dose (p < 0.0005, p = 0.0037 respectively) significantly influenced progression rate. A margin dose of ≥17 Gy was noted to influence the adenoma progression rate in the entire cohort (p = 0.003). Silent corticotroph staining represents an independent factor for adenoma progression and hypopituitarism after SRS. A higher margin dose may convey a greater chance of TCR.

15. Stereotactic Radiosurgery for Cushing Disease: Results of an International, Multicenter Study

Stereotactic Radiosurgery for Cushing Disease: Results of an International, Multicenter Study

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Context: Cushing disease (CD) due to adrenocorticotrophic hormone–secreting pituitary tumors can be a management challenge.

Objective: To better understand the outcomes of stereotactic radiosurgery (SRS) for CD and define its role in management.

Design: International, multicenter, retrospective cohort analysis.

Setting: Ten medical centers participating in the International Gamma Knife Research Foundation.

Patients: Patients with CD with >6 months endocrine follow-up.

Intervention: SRS using Gamma Knife radiosurgery.

Main Outcome Measures: The primary outcome was control of hypercortisolism (defined as normalization of free urinary cortisol). Radiologic response and adverse radiation effects (AREs) were recorded.

Results: In total, 278 patients met inclusion criteria, with a mean follow-up of 5.6 years (0.5 to 20.5 years). Twenty-two patients received SRS as a primary treatment of CD. Mean margin dose was 23.7 Gy. Cumulative initial control of hypercortisolism was 80% at 10 years. Mean time to cortisol normalization was 14.5 months. Recurrences occurred in 18% with initial cortisol normalization. Overall, the rate of durable control of hypercortisolism was 64% at 10 years and 68% among patients who received SRS as a primary treatment. AREs included hypopituitarism (25%) and cranial neuropathy (3%). Visual deficits were related to treatment of tumor within the suprasellar cistern ($P = 0.01$), whereas both visual ($P < 0.0001$) and nonvisual cranial neuropathy ($P = 0.02$) were related to prior pituitary irradiation.

Conclusions: SRS for CD is well tolerated and frequently results in control of hypercortisolism. However, recurrences can occur. SRS should be considered for patients with persistent hypercortisolism after pituitary surgery and as a primary treatment in those unfit for surgery. Long-term endocrine follow-up is essential after SRS.

16. Early versus late Gamma Knife radiosurgery following transsphenoidal surgery for nonfunctioning pituitary macroadenomas: a multicenter matched-cohort study

JNS

CLINICAL ARTICLE

Early versus late Gamma Knife radiosurgery following transsphenoidal surgery for nonfunctioning pituitary macroadenomas: a multicenter matched-cohort study

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Objective: Gamma Knife radiosurgery (GKRS) is frequently used to treat residual or recurrent nonfunctioning pituitary macroadenomas. There is no consensus as to whether GKRS should be used early after surgery or if radiosurgery should be withheld until there is evidence of imaging-defined progression of tumor. Given the high incidence of adenoma progression after subtotal resection over time, the present study intended to evaluate the effect of timing of radiosurgery on outcome.

Methods: This is a multicenter retrospective review of patients with nonfunctioning pituitary macroadenomas who underwent transsphenoidal surgery followed by GKRS from 1987 to 2015 at 9 institutions affiliated with the International Gamma Knife Research Foundation. Patients were matched by adenoma and radiosurgical parameters and stratified based on the interval between last resection and radiosurgery. Operative results, imaging data, and clinical outcomes were compared across groups following early (≤ 6 months after resection) or late (> 6 months after resection) radiosurgery.

Results: After matching, 222 patients met the authors' study criteria (from an initial collection of 496 patients) and were grouped based on early ($n = 111$) or late ($n = 111$) GKRS following transsphenoidal

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surgery. There was a greater risk of tumor progression after GKRS ($p = 0.013$) and residual tumor ($p = 0.038$) in the late radiosurgical group over a median imaging follow-up period of 68.5 months. No significant difference in the occurrence of post-GKRS endocrinopathy was observed ($p = 0.68$). Thirty percent of patients without endocrinopathy in the early cohort developed new endocrinopathies during the follow-up period versus 27% in the late cohort ($p = 0.84$). Fourteen percent of the patients in the early group and 25% of the patients in the late group experienced the resolution of endocrine dysfunction after original presentation ($p = 0.32$).

Conclusions: In this study, early GKRS was associated with a lower risk of radiological progression of subtotaly resected nonfunctioning pituitary macroadenomas compared with expectant management followed by late radiosurgery. Delaying radiosurgery may increase patient risk for long-term adenoma progression. The timing of radiosurgery does not appear to significantly affect the rate of delayed endocrinopathy.

17. Outcomes of stereotactic radiosurgery for foramen magnum meningiomas: an international multicenter study

JNS

CLINICAL ARTICLE

Outcomes of stereotactic radiosurgery for foramen magnum meningiomas: an international multicenter study

Gautam U. Mehta, MD,¹ Georgios Zenonos, MD,² Mohana Rao Patibandla, MCh,¹ Chung Jung Lin, MD,³ Amparo Wolf, MD, PhD,⁴ Inga Grills, MD,⁵ David Mathieu, MD,⁶ Brendan McShane, BS,⁷ John Y. Lee, MD,⁷ Kevin Blas, MD,⁵ Douglas Kondziolka, MD,⁴ Cheng-Chia Lee, MD,⁸ L. Dade Lunsford, MD,² and Jason P. Sheehan, MD, PhD¹

Objective: Meningiomas are the most common benign extramedullary lesions of the foramen magnum; however, their optimal management remains undefined. Given their location, foramen magnum meningiomas (FMMs) can cause significant morbidity, and complete microsurgical removal can be challenging. Anterior and anterolateral FMMs carry greater risks with surgery, but they comprise the majority of these lesions. As an alternative to resection, stereotactic radiosurgery (SRS) has been used to treat FMMs in small case series. To more clearly define the outcomes of SRS and to delineate a rational management paradigm for these lesions, the authors analyzed the safety and efficacy of SRS for FMM in an international multicenter trial.

Methods: Seven medical centers participating in the International Gamma Knife Research Foundation (IGKRF) provided data for this retrospective cohort study. Patients who were treated with Gamma Knife radiosurgery and whose clinical and radiological follow-up was longer than 6 months were eligible for study inclusion. Data from pre- and post-SRS radiological and clinical evaluations were analyzed. Stereotactic radiosurgery treatment variables were recorded.

Results: Fifty-seven patients (39 females and 18 males, with a median age of 64 years) met the study inclusion criteria. Thirty-two percent had undergone prior microsurgical resection. Patients most frequently presented with cranial neuropathy (39%), headache (35%), numbness (32%), and ataxia (30%). Median pre-SRS tumor volume was 2.9 cm³. Median SRS margin dose was 12.5 Gy (range 10–16 Gy). At the last follow-up after SRS, 49% of tumors were stable, 44% had regressed, and 7% had progressed. Progression-free survival rates at 5 and 10 years were each 92%. A greater margin dose was associated with a significantly increased likelihood of tumor regression, with 53% of tumors treated with > 12 Gy regressing. Fifty-two percent of symptomatic patients noted some clinical improvement. Adverse radiation effects were limited to hearing loss and numbness in 1 patient (2%).

Conclusions: Stereotactic radiosurgery for FMM frequently results in tumor control or tumor regression, as well as symptom improvement. Margin doses > 12 Gy were associated with increased rates of tumor regression. Stereotactic radiosurgery was generally safe and well tolerated. Given its risk-benefit

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profile, SRS may be particularly useful in the management of small- to moderate-volume anterior and anterolateral FMMs.

18. Stereotactic radiosurgery for jugular foramen schwannomas: an international multicenter study

JNS

CLINICAL ARTICLE

Stereotactic radiosurgery for jugular foramen schwannomas: an international multicenter study

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Objective: For some jugular foramen schwannomas (JFSs), complete resection is possible but may be associated with significant morbidity. Stereotactic radiosurgery (SRS) is a minimally invasive alternative or adjunct to microsurgery for JFSs. The authors reviewed clinical and imaging outcomes of SRS for patients with these tumors.

Methods: Nine participating centers of the International Gamma Knife Research Foundation identified 92 patients who underwent SRS between 1990 and 2013. Forty-one patients had prior subtotal microsurgical resection. The median interval between previous surgery and SRS was 15 months (range 0.5–144 months). Eighty-four patients had preexisting cranial nerve (CN) symptoms and signs. The median tumor volume was 4.1 cm³ (range 0.8–22.6 cm³), and the median margin dose was 12.5 Gy (range 10–18 Gy). Patients with neurofibromatosis were excluded from this study.

Results: The median follow-up was 51 months (range 6–266 months). Tumors regressed in 47 patients, remained stable in 33, and progressed in 12. The progression-free survival (PFS) was 93% at 3 years, 87% at 5 years, and 82% at 10 years. In the entire series, only a dumbbell shape (extension extracranially via the jugular foramen) was significantly associated with worse PFS. In the group of patients without prior microsurgery (n = 51), factors associated with better PFS included tumor volume < 6 cm³ (p = 0.037) and non-dumbbell-shaped tumors (p = 0.015). Preexisting cranial neuropathies improved in 27 patients, remained stable in 51, and worsened in 14. The CN function improved after SRS in 12% of patients at 1 year, 24% at 2 years, 27% at 3 years, and 32% at 5 years. Symptomatic adverse radiation effects occurred in 7 patients at a median of 7 months after SRS (range 5–38 months). Six patients underwent repeat SRS at a median of 64 months (range 44–134 months). Four patients underwent resection at a median of 14 months after SRS (range 8–30 months).

Conclusions: Stereotactic radiosurgery proved to be a safe and effective primary or adjuvant management approach for JFSs. Long-term tumor control rates and stability or improvement in CN function were confirmed.

Current Retrospective Trials

- Volume-Stage SRS for Large AVMs. PI: Zachary
- Dural AVE. PI: Starke recruiting.
- Ependymoma. PI: Kano
- Repeat GK for AVMs. PI: Kano
- AVM ARE and delayed cyst formation. PI Kano
- Gamma Knife SRS in Small Cell Lung Cancer. PI: Cifarelli
- SRS cavernous malformations: PI: Kano,
- Gamma Ventral Capsulotomy for OCD PI: Gupta
- SRS in a distal aneurysm not associated with AVM. PI: Liscak
- SRS for Trigeminal Schwannoma. PI: Niranjan,

Current Prospective Clinical Trials

- 12-02: Multicenter Phase II Study of border zone SR with Bevacizumab chemotherapy in patients with recurrent or progressive glioblastoma multiforme (PI: Dr. Niranjana): Recruitment continues at the University of Pittsburgh

IGKRF Membership Update

At present IGKRF has 32 active members and 7 provisional members (listed below). In year 2017 following members joined the IGKRF.

New Full Members

- Sunnybrook Odette Cancer Centre of the University of Toronto
- Mayo Clinic Jacksonville, Jacksonville, Fla.
- University of Miami

Provisional Members

- Gazi Universitesi Tip Fakultesi Beyin ve Sinir Cerrahisi AD, Ankara, Turkey
- Prince Sultan Military Medical City, Riyadh, Saudi Arabia
- University of Alberta Hospital, Edmonton, Canada

IGKRF Biennial Meeting 2019

The next biennial meeting of IGKRF will be held in 2019. Dates and Venue will be announced soon.

Spotlight: Sunnybrook Odette Cancer Centre, University of Toronto

The Sunnybrook Health Sciences Center has a long tradition of SRS stemming from the pioneering work of Dr. Michael Schwartz. Our Cancer Center, the Odette Cancer Center, is the 6th largest in North America. On June 13th 2017 we performed the first GK Icon treatment in Canada. We have a fully functional SRS and Neuro-Oncology program led by Dr. Arjun Sahgal from Radiation Oncology, Dr. James Perry from Neuro-Oncology and Dr. Todd Mainprize from Neurosurgery. Since November 2016, we have treated over 400 patients on our GK unit, and approximately 1700 targets. Our research focus is on multiple metastases and Icon, advancing the CBCT imaging system and inverse treatment planning solution. In addition, we have a major advanced functional MR imaging program for response using Chemical Exchange Saturation Transfer MR Imaging and hyperpolarized C13. Research into integrating MRGFUS and blood-brain-barrier opening is driven by Dr. Nir Lipsman and Dr. Mainprize. We also lead the North American Icon Research Group mandated to technical development of the Icon.



Sunnybrook staff ►