



# International Radiosurgery Research Foundation

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

## Spring 2019

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## Chairman's Message

The International Gamma Knife Research Foundation is now the International Radiosurgery Research Foundation (IRRF)! As the clinical and academic landscapes have changed over the last several years, so have we. First, changing from a regional to an international organization (North American Gamma Knife Research Foundation to IGKRF), and now to a radiosurgery platform agnostic research foundation. This change has several advantages for us as well as for radiosurgical academia, in general. By extending our research expertise to all radiosurgical platforms, we can assess outcomes across platforms and within platforms, thereby expanding multicenter studies of relatively rare disorders, and extending membership to medical centers that are expert at performing radiosurgery, but don't have a Gamma Knife. Further, as Gamma Knife was limited largely to cranial radiosurgery, we can now extend our research portfolio to spinal radiosurgery. Additionally, as an organization, we will be less reliant on one vendor for research and meeting support. Lastly, it will allow us to better partner with other organizations which are already platform agnostic, such as the International Stereotactic Research Society (ISRS).

The next meeting of the IRRF will be held on June 18-20, 2020, at the Long Island Marriott Hotel on Long Island, New York (just outside of New York City). The meeting will be in collaboration with the ISRS and—leveraging the resources and expertise of the two organizations—we envision robust scientific and workshop programs. The scientific co-directors of the meeting will be Michael Schulder (site host) and Douglas Kondziolka representing IRRF and John Suh representing ISRS.

Also, speaking of change, we have introduced a new level of membership (in addition to provisional and full): associate membership. We are also looking to offer Center of Radiosurgery Research Excellence recognition to academic centers. Associate membership is valuable for centers that have minimal funding including international sites. There is a \$1000 initiation fee which will cover membership dues for the first two years and then \$500 dues per year. Membership would then be contingent upon submission of cases to collaborative studies. Associate members can participate in research projects by contributing cases and will be listed as co-authors. There remain some real advantages to being a Full Member (FM), however:

- Only FMs can be 1st or senior author,
- Only FMs can put a trial forward,
- Only FMs can serve on committees,
- Only FMs can participate in prospective trials,
- FMs are eligible to receive IRRF's center of radiosurgery research excellence recognition, renewable every three years,
- Only FMs can receive IRRF grants.

Centers of Radiosurgery Research Excellence –this recognition will be awarded and will be renewed every three years) to full members. The following criteria will be considered:

- Scholarly activity (academic output from the center every year)
- Volume of cases (a minimum of 100 cases per year)
- Participation in collaborative trials, and
- Presence of multidisciplinary team (neurosurgeon, radiation oncologist, medical physicist, and allied staff) at the site.

Stay tuned, as we work out the details and, hopefully, roll out the Center of Excellence initiative this year.

**Gene Barnett, MD**

## International Radiosurgery Research Foundation

The International Radiosurgery Research Foundation (IRRF) was organized in 2008 and consists of academic and clinical centers of excellence where brain Stereotactic Radiosurgery is performed. The primary goal of the IRRF is to facilitate retrospective and prospective clinical trials and outcomes analysis that evaluate the role of 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 60 multicenter retrospective studies have been published by IRRF members. Seventeen multi-center studies were published in year 2018.

IRRF'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 Radiosurgery, and provide communication and administrative support staff. The member organizations of IRRF are represented by neurological surgeons, radiation oncologists, medical physicists and researchers from leading academic national and international medical facilities.

### Recent Developments

- Considering request from various radiosurgery centers in April 2018, board members decided to expand the scope of the foundation and changed the name of society to International Radiosurgery Research Foundation (IRRF) from International Gamma Knife Research Foundation (IGKRF).
- It was also decided to have two tiers of membership. Full members and associate members.
- IRRF Research Grant was also introduced.

## IRRF Retrospective Studies Published in 2018

### Stereotactic Radiosurgery for Pediatric Versus Adult Brain Arteriovenous Malformations A Multicenter Study

Ching-Jen Chen, MD; Dale Ding, MD; Hideyuki Kano, MD; David Mathieu, MD;  
Douglas Kondziolka, MD; Caleb Feliciano, MD; Rafael Rodriguez-Mercado, MD;  
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on behalf of the International Gamma Knife Research Foundation

**Background and Purpose:** The aim of this international, multicenter, retrospective matched cohort study is to directly compare the outcomes after stereotactic radiosurgery (SRS) for brain arteriovenous malformations (AVM) in pediatric versus adult patients.

**Methods:** We performed a retrospective review of patients with AVM who underwent SRS at 8 institutions participating in the International Gamma Knife Research Foundation from 1987 to 2014. Patients were categorized into pediatric (<18 years of age) and adult (≥18 years of age) cohorts and matched in a 1:1 ratio using propensity scores. Favorable outcome was defined as AVM obliteration, no post-SRS hemorrhage, and no permanently symptomatic radiation-induced changes.

**Results:** From a total of 2191 patients who were eligible for inclusion in the overall study cohort, 315 were selected for each of the matched cohorts. There were no significant differences between matched pediatric versus adult cohorts with respect to the rates of favorable outcome (59% versus 58%;  $P=0.936$ ), AVM obliteration (62% versus 63%;  $P=0.934$ ), post-SRS hemorrhage (9% versus 7%;  $P=0.298$ ), radiological radiation-induced changes (26% versus 26%;  $P=0.837$ ), symptomatic radiation-induced changes (7% versus 9%;  $P=0.383$ ), or permanent radiation-induced changes (2% versus 3%;  $P=0.589$ ). The all-cause mortality rate was significantly lower in the matched pediatric cohort (3% versus 10%;  $P=0.003$ ).

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**Conclusions:** The outcomes after SRS for comparable AVMs in pediatric versus adult patients were not found to be appreciably different. SRS remains a reasonable treatment option for appropriately selected pediatric patients with AVM, who harbor a high cumulative lifetime hemorrhage risk. Age seems to be a poor predictor of AVM outcomes after SRS.

## ORIGINAL ARTICLE



### Effect of Advanced Age on Stereotactic Radiosurgery Outcomes for Brain Arteriovenous Malformations: A Multicenter Matched Cohort Study

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**Background:** The effect of age on adult brain arteriovenous malformation (AVM) outcomes after stereotactic radiosurgery (SRS) remains unclear. The aim of this study is to compare AVM outcomes between elderly (age  $\geq 60$  years) and nonelderly adult patients.

**Methods:** We retrospectively reviewed pooled data comprising patients who underwent SRS for AVMs between 1987 and 2014 at 8 centers participating in the International Gamma Knife Research Foundation. Adult (age  $\geq 18$  years) patients with  $\geq 12$  months follow-up were dichotomized into elderly and nonelderly cohorts, and matched in a 1:1 ratio. Favorable outcome was AVM obliteration without permanent symptomatic radiation-induced changes (RIC) or post-SRS hemorrhage.

**Results:** The study cohort consisted of 1845 patients (188 elderly vs. 1657 nonelderly) who met the inclusion criteria, and subsequent matching resulted in 181 patients in each cohort. In the matched cohorts, rates of obliteration (54.7% vs. 64.6%;  $P = 0.054$ ) favorable outcome (51.4% vs. 61.3%;  $P = 0.056$ ) were no different between the elderly and nonelderly cohorts. The rates of post-SRS hemorrhage (9.9% vs. 5.5%;  $P = 0.115$ ), RIC (26.5% vs. 30.9%;  $P = 0.353$ ), symptomatic RIC (9.4% vs. 9.4%;  $P = 1.000$ ), and permanent symptomatic RIC (3.3% vs. 2.2%;  $P = 0.750$ ) were also not significantly different between the elderly and nonelderly cohorts. Elderly patients with AVM did have a significantly higher rate of all-cause mortality (27.7% vs. 5.5%;  $P < 0.001$ ).

**Conclusions:** Advanced age does not seem to significantly affect obliteration or complication rates after SRS for AVMs. Although the decision to recommend intervention for AVMs in the elderly population is multifactorial, SRS may be a viable modality when treatment is deemed appropriate.



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Clinical study

### Evolution in the role of stereotactic radiosurgery in patients with multiple brain metastases: An international survey

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**Objective:** Currently no firm consensus exists regarding utilization of stereotactic radiosurgery (SRS) alone versus whole brain radiation (WBRT)+/-SRS in patients with multiple brain metastases. The International Gamma Knife Research Foundation conducted a survey to review international practice patterns.

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**Methods:** Through 2 international radiosurgery societies, clinicians who are involved in the radio-surgical management of patients with brain metastases were invited to complete a questionnaire. Respondents selected therapeutic options based on brief case vignettes and could select (1) SRS alone, (2) SRS with adjuvant WBRT, (3) WBRT alone, or (4) omission of upfront local radiation.

**Results:** A total of 71 respondents replied to the survey, including 41 radiation oncologists (57%), 24 neurosurgeons (34%), and 6 (8%) other clinicians. For a patient with 7 brain metastases (NSCLC), all under 1cm, and stable extracranial disease, 77% would perform SRS alone and 17% would recommend WBRT alone. For a patient with 7 or more brain metastases, the majority selected SRS alone, irrespective of tumor histology ( $p>0.5$ ). However, neurosurgeons would more often utilize SRS alone or SRS combined with WBRT compared to radiation oncologists ( $p=0.002$ ). Key clinical factors in selection were KPS (82% of respondents), total tumor volume (81%), number (80%), and less-so histology (42%).

**Conclusion:** Regardless of number of metastases, patients with small total volume of brain disease, high KPS, or who are receiving novel therapies are often recommended to undergo SRS. Neurosurgeons more often recommend SRS, emphasizing the importance of additional studies to clarify the role of SRS in these patients.

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CLINICAL ARTICLE

## Upfront Gamma Knife radiosurgery for Cushing's disease and acromegaly: a multicenter, international study

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**Objective:** Gamma Knife radiosurgery (GKS) is typically used after failed resection in patients with Cushing's disease (CD) and acromegaly. Little is known about the upfront role of GKS for patients with CD and acromegaly. In this study, the authors examine the outcome of upfront GKS for patients with these functioning adenomas.

**Methods:** An international group of 7 Gamma Knife centers sent pooled data from 46 patients (21 with CD and 25 with acromegaly) undergoing upfront GKS to the coordinating center of the study for analysis. Diagnosis was established on the basis of clinical, endocrine, and radiological studies. All patients were treated on a common radiosurgical platform and longitudinally followed for tumor control, endocrine remission, and hypopituitarism. Patients received a tumor median margin dose of 25 Gy (range 12-40.0 Gy) at a median isodose of 50%.

**Results:** The median endocrine follow-up was 69.5 months (range 9-246 months). Endocrine remission was achieved in 51% of the entire cohort, with 28% remission in acromegaly and 81% remission for those with CD at the 5-year interval. Patients with CD achieved remission earlier as compared to those with acromegaly ( $p = 0.0005$ ). In patients post-GKS, the pituitary adenoma remained stable (39%) or reduced (61%) in size. Hypopituitarism occurred in 9 patients (19.6%), and 1 (2.2%) developed third cranial nerve (CN III) palsy. Eight patients needed further intervention, including repeat GKS in 6 and transsphenoidal surgery in 2.

**Conclusion:** Upfront GKS resulted in good tumor control as well as a low rate of adverse radiation effects in the whole group. Patients with CD achieved a faster and far better remission rate after upfront GKS in comparison to patients with acromegaly. GKS can be considered as an upfront treatment in carefully selected patients with CD who are unwilling or unable to undergo resection, but it has a more limited role in acromegaly.

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## RESEARCH—HUMAN—CLINICAL STUDIES

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## Repeat Stereotactic Radiosurgery for Progressive or Recurrent Vestibular Schwannomas

**BACKGROUND:** Stereotactic radiosurgery (SRS) is a highly effective management approach for patients with vestibular schwannomas (VS), with 10-yr control rates up to 98%. When it fails, however, few data are available to guide management.

**OBJECTIVE:** To perform a retrospective analysis of patients who underwent 2 SRS procedures on the same VS to assess the safety and efficacy of this practice.

**METHODS:** This study was opened to centers of the International Gamma Knife Research Foundation (IGKRF). Data collected included patient characteristics, clinical symptoms at

**Background:** Stereotactic radiosurgery (SRS) is a highly effective management approach for patients with vestibular schwannomas (VS), with 10-yr control rates up to 98%. When it fails, however, few data are available to guide management.

**Objective:** To perform a retrospective analysis of patients who underwent 2 SRS procedures on the same VS to assess the safety and efficacy of this practice.

**Methods:** This study was opened to centers of the International Gamma Knife Research Foundation (IGKRF). Data collected included patient characteristics, clinical symptoms at the time of SRS, radiosurgery dosimetric data, imaging response, clinical evolution, and survival. Actuarial analyses of tumor responses were performed.

**Results:** Seventy-six patients from 8 IGKRF centers were identified. Median follow-up from the second SRS was 51.7 mo. Progression after the first SRS occurred at a median of 43 mo. Repeat SRS was performed using a median dose of 12 Gy. Actuarial tumor control rates at 2, 5, and 10 yr following the second SRS were 98.6%, 92.2%, and 92.2%, respectively. Useful hearing was present in 30%, 8%, and 5% of patients at first SRS, second SRS, and last follow-up, respectively. Seventy-five percent of patients reported stable or improved symptoms following the second SRS. Worsening of facial nerve function attributable to SRS occurred in 7% of cases. There were no reports of radionecrosis, radiation-associated edema requiring corticosteroids, radiation-related neoplasia, or death attributable to the repeat SRS procedure.

**Conclusion:** Patients with progressing VS after radiosurgery can be safely and effectively managed using a second SRS procedure.

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## CLINICAL STUDY



## Repeat stereotactic radiosurgery for Cushing's disease: outcomes of an international, multicenter study

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Stereotactic radiosurgery (SRS) is frequently used for Cushing's disease (CD) after failed pituitary surgery. Management of patients with persistent CD after failed SRS is complex, as the alternative therapeutic options harbor significant risks. The outcomes of repeat pituitary radiosurgery, however, have not been described. We sought to determine the outcomes of repeat SRS in patients with CD. We pooled data

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from five institutions participating in the International Gamma Knife Research Foundation for patients with recurrent or persistent CD  $\geq 12$  months after initial SRS. Patients were included in the study if they had  $\geq 6$  months endocrine follow-up after repeat SRS. Twenty patients were included in the study. Repeat single-session SRS was performed 1.3–9.7 years after initial SRS. Median endocrine follow-up was 6.6 years (1.4–19.1 years). Median margin dose was 20 Gy (range 10.8–35 Gy). Endocrine remission after second SRS was noted in 12 patients (60%), with a median time to remission of 6 months (range 2–64 months). Biochemical recurrence occurred in two patients (17%) after initial remission. Overall, the cumulative rates of durable endocrine remission at 5 and 10 years were 47 and 53%, respectively. Two patients (10%) experienced adverse radiation effects, including transient visual loss and permanent diplopia. Repeat SRS achieves lasting biochemical remission in approximately half of patients with CD refractory to both prior microsurgery and SRS. Because of the morbidity of refractory or recurrent CD, repeat SRS should be considered for carefully selected patients with hypercortisolism confirmed one or more years after initial SRS.

## ORIGINAL ARTICLE

 Check for updates

### Technique of Whole-Sellar Stereotactic Radiosurgery for Cushing Disease: Results from a Multicenter, International Cohort Study

Matthew J. Shepard<sup>1</sup>, Gautam U. Mehta<sup>1,2</sup>, Zhiyuan Xu<sup>1</sup>, Hideyuki Kano<sup>3</sup>, Nathaniel Sisterson<sup>3</sup>, Yan-Hua Su<sup>4</sup>, Michal Krsek<sup>5</sup>, Ahmed M. Nabeef<sup>6</sup>, Amr El-Shehaby<sup>7</sup>, Khaled A. Kareem<sup>8</sup>, Nuria Martinez-Moreno<sup>9</sup>, David Mathieu<sup>10</sup>, Brendan J. McShane<sup>11</sup>, Kevin Blas<sup>12</sup>, Douglas Kondziolka<sup>13</sup>, Inga Grills<sup>12</sup>, John Y. Lee<sup>11</sup>, Roberto Martinez-Alvarez<sup>9</sup>, Wael A. Reda<sup>7</sup>, Roman Liscak<sup>14</sup>, Cheng-Chia Lee<sup>8</sup>, L. Dade Lunsford<sup>8</sup>, Mary Lee Vance<sup>15</sup>, Jason P. Sheehan<sup>1</sup>

**Background:** Stereotactic radiosurgery (SRS) is used to manage patients with Cushing disease (CD) who have failed surgical/medical management. Because many patients with recurrent/persistent CD lack an identifiable adenoma on neuroimaging, whole-sellar SRS has been increasingly used. Thus, we sought to define the outcomes of patients undergoing whole-sellar SRS.

**Methods:** An international, multicenter, retrospective cohort design was used to define clinical/endocrine outcomes for patients undergoing whole-sellar SRS for CD. Propensity-score matching was used to compare patients undergoing whole-sellar SRS and patients who underwent discrete adenoma-targeted SRS.

**Results:** A total of 68 patients underwent whole-sellar SRS, with a mean endocrine follow-up of 5.3 years. The mean treatment volume was 2.6 cm<sup>3</sup>, and the mean margin dose was 22.4 Gy. The 5-year actuarial remission rate was 75.9%, and the median time to remission was 12-months. Treatment volumes  $>1.6$  cm<sup>3</sup> were associated with shorter times to remission ( $P < 0.05$ ). The 5-year recurrence-free survival rate was 86.0%. Decreased margin and maximum treatment doses were associated with recurrence ( $P < 0.05$ ). New pituitary hormone deficiency occurred in 15 patients (22.7%). An additional 210 patients were identified who underwent adenoma-targeted SRS. There was no difference in remission rate, time to remission, recurrence-free survival or new endocrinopathy development between patients who underwent whole-sellar SRS and those who underwent discrete adenoma-targeted SRS.

**Conclusion:** Whole-sellar GKRS is effective in controlling CD when an adenoma is not clearly defined on imaging or when an invasive adenoma is suspected at the time of initial surgery. Patients who undergo whole-sellar SRS have outcomes and rates of new pituitary hormone deficiency similar to those of patients who undergo discrete adenoma-targeted GKRS.

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## Stereotactic radiosurgery for arteriovenous malformations of the basal ganglia and thalamus: an international multicenter study

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**Objective:** Arteriovenous malformations (AVMs) of the basal ganglia (BG) and thalamus are associated with elevated risks of both hemorrhage if left untreated and neurological morbidity after resection. Therefore, stereotactic radiosurgery (SRS) has become a mainstay in the management of these lesions, although its safety and efficacy remain incompletely understood. The aim of this retrospective multicenter cohort study was to evaluate the outcomes of SRS for BG and thalamic AVMs and determine predictors of successful endpoints and adverse radiation effects.

**Methods;** The authors retrospectively reviewed data on patients with BG or thalamic AVMs who had undergone SRS at eight institutions participating in the International Gamma Knife Research Foundation (IGKRF) from 1987 to 2014. Favorable outcome was defined as AVM obliteration, no post-SRS hemorrhage, and no permanently symptomatic radiation-induced changes (RICs). Multivariable models were developed to identify independent predictors of outcome.

**Results;** The study cohort comprised 363 patients with BG or thalamic AVMs. The mean AVM volume and SRS margin dose were 3.8 cm<sup>3</sup> and 20.7 Gy, respectively. The mean follow-up duration was 86.5 months. Favorable outcome was achieved in 58.5% of patients, including obliteration in 64.8%, with rates of post-SRS hemorrhage and permanent RIC in 11.3% and 5.6% of patients, respectively. Independent predictors of favorable outcome were no prior AVM embolization ( $p = 0.011$ ), a higher margin dose ( $p = 0.008$ ), and fewer isocenters ( $p = 0.044$ ).

**Conclusions;** SRS is the preferred intervention for the majority of BG and thalamic AVMs. Patients with morphologically compact AVMs that have not been previously embolized are more likely to have a favorable outcome, which may be related to the use of a higher margin dose.

### ARTICLE IN PRESS

#### ORIGINAL ARTICLE

### Seizure Presentation in Patients with Brain Arteriovenous Malformations Treated with Stereotactic Radiosurgery: A Multicenter Study

Ching-Jen Chen<sup>1</sup>, Leah M. Shabo<sup>1</sup>, Dale Ding<sup>2</sup>, Natasha Ironside<sup>2</sup>, Hideyuki Kano<sup>4</sup>, David Mathieu<sup>5</sup>, Douglas Kondziolka<sup>6</sup>, Caleb Feliciano<sup>7</sup>, Rafael Rodriguez-Mercado<sup>7</sup>, Inga S. Grills<sup>9</sup>, Gene Barnett<sup>9</sup>, L. Dade Lunsford<sup>4</sup>, Jason P. Sheehan<sup>1</sup>, on behalf of the International Radiosurgery Research Foundation

**Background:** Seizures are the second most common clinical presentation in patients with brain arteriovenous malformations (AVMs) and the most common presentation of unruptured AVMs. The aim of the present multicenter, retrospective cohort study was to identify the predictors of seizure presentation in patients with AVM who had undergone stereotactic radiosurgery (SRS).

**Methods:** We performed a retrospective review of patients with AVM who had been treated with SRS at 8 participating International Radiosurgery Research Foundation sites. The patient and AVM charac-

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teristics were compared between those with and without seizure presentation in univariable and multivariable models. A subgroup analysis of patients with cortical AVMs was performed.

**Results:** The study cohort included 2333 patients with AVM, including 419 (18%) with and 1914 (82%) without a seizure presentation. Previous AVM resection (odds ratio [OR], 7.65;  $P = 0.001$ ), a lack of previous AVM hemorrhage (OR, 0.004;  $P < 0.001$ ), a cortical AVM location (OR, 1559.42;  $P < 0.001$ ), a lower Spetzler-Martin grade (OR, 0.51;  $P = 0.007$ ), and a higher Virginia radiosurgery AVM score (OR, 1.46;  $P = 0.008$ ) were independent predictors of seizure presentation. The rate of seizure presentation in patients with cortical AVMs was 27%. Previous AVM resection (OR, 8.36;  $P < 0.001$ ), a lack of previous AVM hemorrhage (OR, 0.004;  $P < 0.001$ ), and temporal AVM location (OR, 4.15;  $P < 0.001$ ) were independent predictors of seizure presentation for cortical AVMs.

**Conclusion:** We identified multiple factors associated with seizure presentation in patients with AVM to undergo SRS. Previous AVM resection, a cortical AVM location, and a lack of previous AVM hemorrhage were the strongest predictors of pre-SRS seizures. The Spetzler-Martin grade and Virginia radiosurgery AVM score might have a role in seizure risk stratification. For cortical AVMs, a temporal lobe location was predictive of seizure presentation.

## RESEARCH—HUMAN—CLINICAL STUDIES

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### Stereotactic Radiosurgery for Acromegaly: An International Multicenter Retrospective Cohort Study

**BACKGROUND:** Stereotactic radiosurgery (SRS) is a treatment option for persistent or recurrent acromegaly secondary to a growth hormone secreting pituitary adenoma, but its efficacy is inadequately defined.

**OBJECTIVE:** To assess, in a multicenter, retrospective cohort study, the outcomes of SRS for acromegaly and determine predictors.

**METHODS:** We pooled and analyzed data from 10 participating institutions of the International Gamma Knife Research Foundation for patients with acromegaly who underwent SRS with endocrine follow-up of  $\geq 6$  mo.

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**Methods:** We pooled and analyzed data from 10 participating institutions of the International Gamma Knife Research Foundation for patients with acromegaly who underwent SRS with endocrine follow-up of  $\geq 6$  mo.

**Results:** The study cohort comprised 371 patients with a mean endocrine follow-up of 79 mo. IGF-1 lowering medications were held in 56% of patients who were on pre-SRS medical therapy. The mean SRS treatment volume and margin dose were 3.0 cm<sup>3</sup> and 24.2 Gy, respectively. The actuarial rates of initial and durable endocrine remission at 10 yr were 69% and 59%, respectively. The mean time to durable remission after SRS was 38 mo. Biochemical relapse after initial remission occurred in 9%, with a mean time to recurrence of 17 mo. Cessation of IGF-1 lowering medication prior to SRS was the only independent predictor of durable remission ( $P = .01$ ). Adverse radiation effects included the development of  $\geq 1$  new endocrinopathy in 26% and  $\geq 1$  cranial neuropathy in 4%.

**Conclusion:** SRS is a definitive treatment option for patients with persistent or recurrent acromegaly after surgical resection. There appears to be a statistical association between the cessation of IGF-1 lowering medications prior to SRS and durable remission.

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## RESEARCH—HUMAN—CLINICAL STUDIES

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## Stereotactic Radiosurgery for Intracranial Ependymomas: An International Multicenter Study

**BACKGROUND:** Stereotactic radiosurgery (SRS) is a potentially important option for intracranial ependymoma patients.

**OBJECTIVE:** To analyze the outcomes of intracranial ependymoma patients who underwent SRS as a part of multimodality management.

**METHODS:** Seven centers participating in the International Gamma Knife Research Foundation identified 89 intracranial ependymoma patients who underwent SRS (113 tumors). The median patient age was 16.3 yr (2.9-80). All patients underwent previous surgical resection and radiation therapy (RT) of their ependymomas and 40 underwent previous chemotherapy. Grade 2 ependymomas were present in 42 patients (52 tumors) and grade 3 ependymomas in 48 patients (61 tumors). The median tumor volume was 2.2 cc (0.03-36.8) and the median margin dose was 15 Gy (9-24).

**RESULTS:** Forty-seven (53%) patients were alive and 42 (47%) patients died at the last follow-up. The overall survival after SRS was 86% at 1 yr, 50% at 3 yr, and 44% at 5 yr. Smaller total tumor volume was associated with longer overall survival ( $P = .006$ ). Twenty-two

**Background:** Stereotactic radiosurgery (SRS) is a potentially important option for intracranial ependymoma patients.

**Objective:** To analyze the outcomes of intracranial ependymoma patients who underwent SRS as a part of multimodality management.

**Methods:** Seven centers participating in the International Gamma Knife Research Foundation identified 89 intracranial ependymoma patients who underwent SRS (113 tumors). The median patient age was 16.3 yr (2.9-80). All patients underwent previous surgical resection and radiation therapy (RT) of their ependymomas and 40 underwent previous chemotherapy. Grade 2 ependymomas were present in 42 patients (52 tumors) and grade 3 ependymomas in 48 patients (61 tumors). The median tumor volume was 2.2 cc (0.03-36.8) and the median margin dose was 15 Gy (9-24).

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**Conclusion:** SRS provides another management option for residual or recurrent progressive intracranial ependymoma patients who have failed initial surgery and RT.

## ARTICLE IN PRESS

## ORIGINAL ARTICLE

### A Propensity Score–Matched Cohort Analysis of Outcomes After Stereotactic Radiosurgery in Older versus Younger Patients with Dural Arteriovenous Fistula: An International Multicenter Study

Nasser Mohammed<sup>2</sup>, Yi-Chieh Hung<sup>2</sup>, Zhiyuan Xu<sup>2</sup>, Robert M. Starke<sup>1</sup>, Hideyuki Kano<sup>3</sup>, John Lee<sup>4</sup>, David Mathieu<sup>5</sup>, Anthony M. Kaufmann<sup>6</sup>, Inga S. Grills<sup>7</sup>, Christopher P. Cifarelli<sup>8</sup>, John A. Vargo<sup>8</sup>, Tomas Chytka<sup>9</sup>, Ladislava Janouškova<sup>9</sup>, Caleb E. Feliciano<sup>10</sup>, Rafael Rodriguez Mercado<sup>10</sup>, L. Dade Lunsford<sup>3</sup>, Jason P. Sheehan<sup>2</sup>

**Objective:** This study aims to evaluate the outcomes of Gamma Knife stereotactic radiosurgery (SRS) for dural arteriovenous fistulas (dAVFs) in older patients ( $\geq 65$  years) compared with younger patients (age  $< 65$  years).

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**Methods:** Two groups with a total of 96 patients were selected from a database of 133 patients with dAVF from 9 international medical centers with a minimum 6 months follow-up. A 1:2 propensity matching was performed by nearest-neighbor matching criteria based on sex, Borden grade, maximum radiation dose given, and location. The older cohort consisted of 32 patients and the younger cohort consisted of 64 patients. The mean overall follow-up in the combined cohort was 42.4 months (range, 6-210 months).

**Results:** In the older cohort, a transverse sinus location was found to significantly predict dAVF obliteration ( $P = 0.01$ ). The post-SRS actuarial 3-year and 5-year obliteration rates were 47.7% and 78%, respectively. There were no cases of post-SRS hemorrhage. In the younger cohort, the cavernous sinus location was found to significantly predict obliteration ( $P = 0.005$ ). The 3-year and 5-year actuarial obliteration rates were 56% and 70%, respectively. Five patients (7.8%) hemorrhaged after SRS. Margin dose  $\geq 25$  Gy was predictive of unfavorable outcome. The obliteration rate ( $P = 0.3$ ), post-SRS hemorrhage rate ( $P = 0.16$ ), and persistent symptoms after SRS ( $P = 0.83$ ) were not statistically different between the 2 groups.

**Conclusion:** SRS achieves obliteration in most older patients with dAVF, with an acceptable rate of complication. There was no increased risk of postradiosurgery complications in the older cohort compared with the younger patients.

## ARTICLE IN PRESS

## ORIGINAL ARTICLE

### Outcomes After Gamma Knife Stereotactic Radiosurgery in Pediatric Patients with Cushing Disease or Acromegaly: A Multi-Institutional Study

Adesh Shrivastava<sup>1,2</sup>, Nasser Mohammed<sup>1</sup>, Zhiyuan Xu<sup>1</sup>, Roman Liščák<sup>2</sup>, Mikulas Kosak<sup>2</sup>, Michal Krsek<sup>2</sup>, Khaled Abdel Karim<sup>3</sup>, Cheng-Chia Lee<sup>4</sup>, Nuria Martinez-Moreno<sup>5</sup>, Mary Lee Vance<sup>6</sup>, L. Dade Lunsford<sup>7</sup>, Jason P. Sheehan<sup>1</sup>

**Objective:** Pituitary adenomas comprise about 3% of all intracranial tumors in pediatric patients. This study examines the role of stereotactic radiosurgery in the management of pediatric acromegaly or patients with Cushing disease (CD).

**Methods:** From an international consortium, we retrospectively collected treatment and outcome data on pediatric adrenocorticotrophic hormone and growth hormone-secreting pituitary adenomas treated with Gamma Knife radiosurgery (GKRS). There were a total of 36 patients including 24 with CD and 12 with acromegaly. The data were analyzed to assess outcomes including tumor control, endocrine remission, and adverse effects. Statistical analysis was performed to determine correlation between clinical/treatment parameters and outcomes.

**Results:** At the last follow-up after GKRS, endocrine remission rates for CD and acromegaly were 80% and 42%, respectively. Tumor control was achieved in 87.5% of patients with CD and in 42% of patients with acromegaly. New pituitary hormone deficiency occurred in 7 of the 36 patients at a median time of 18 months after GKRS (range, 12-81 months). The predictive factors for endocrine remission were age  $<15$  years ( $P = 0.015$ ) and margin dose ( $P = 0.042$ ). The median endocrine follow-up was 63.7 months (range, 7-246 months).

**Conclusions:** GKRS affords reasonable rates of endocrine remission and tumor control in most pediatric patients with functioning adenomas. The most common post-GKRS complication was hypopituitarism, although this occurred in only a few patients. Given the larger at-risk period for pediatric patients, further study is required to evaluate for delayed recurrences and hypopituitarism.

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## Evaluation of stereotactic radiosurgery for cerebral dural arteriovenous fistulas in a multicenter international consortium

Robert M. Starke, MD, MSc,<sup>1</sup> David J. McCarthy, MSc,<sup>1</sup> Ching-Jen Chen, MD,<sup>2</sup> Hideyuki Kano, MD, PhD,<sup>3</sup> Brendan McShane, BS,<sup>4</sup> John Lee, MD,<sup>4</sup> David Mathieu, MD,<sup>5</sup> Lucas T. Vasas, BS,<sup>6</sup> Anthony M. Kaufmann, MD, MSc, FRCSC,<sup>6</sup> Wei Gang Wang, MD,<sup>7</sup> Inga S. Grills, MD,<sup>7</sup> Mohana Rao Patibandla, MCh,<sup>2</sup> Christopher P. Cifarelli, MD, PhD,<sup>8</sup> Gabriella Paisan, MD,<sup>2</sup> John A. Vargo, MD,<sup>9</sup> Tomas Chytka, MD,<sup>10</sup> Ladislava Janouskova, MD,<sup>10</sup> Caleb E. Feliciano, MD,<sup>11</sup> Rafael Rodriguez-Mercado, MD,<sup>11</sup> Daniel A. Tonetti, MD,<sup>3</sup> L. Dade Lunsford, MD,<sup>3</sup> and Jason P. Sheehan, MD, PhD<sup>2</sup>

**Objective:** In this multicenter study, the authors reviewed the results obtained in patients who underwent Gamma Knife radiosurgery (GKRS) for dural arteriovenous fistulas (dAVFs) and determined predictors of outcome.

**Methods:** Data from a cohort of 114 patients who underwent GKRS for cerebral dAVFs were compiled from the International Gamma Knife Research Foundation. Favorable outcome was defined as dAVF obliteration and no posttreatment hemorrhage or permanent symptomatic radiation-induced complications. Patient and dAVF characteristics were assessed to determine predictors of outcome in a multivariate logistic regression analysis; dAVF-free obliteration was calculated in a competing-risk survival analysis; and Youden indices were used to determine optimal radiosurgical dose.

**Results:** A mean margin dose of 21.8 Gy was delivered. The mean follow-up duration was 4 years (range 0.5–18 years). The overall obliteration rate was 68.4%. The postradiosurgery actuarial rates of obliteration at 3, 5, 7, and 10 years were 41.3%, 61.1%, 70.1%, and 82.0%, respectively. Post-GKRS hemorrhage occurred in 4 patients (annual risk of 0.9%). Radiation-induced imaging changes occurred in 10.4% of patients; 5.2% were symptomatic, and 3.5% had permanent deficits. Favorable outcome was achieved in 63.2% of patients. Patients with middle fossa and tentorial dAVFs (OR 2.4,  $p = 0.048$ ) and those receiving a margin dose greater than 23 Gy (OR 2.6,  $p = 0.030$ ) were less likely to achieve a favorable outcome. Commonly used grading scales (e.g., Borden and Cognard) were not predictive of outcome. Female sex (OR 1.7,  $p = 0.03$ ), absent venous ectasia (OR 3.4,  $p < 0.001$ ), and cavernous carotid location (OR 2.1,  $p = 0.019$ ) were predictors of GKRS-induced dAVF obliteration.

**Conclusions:** GKRS for cerebral dAVFs achieved obliteration and avoided permanent complications in the majority of patients. Those with cavernous carotid location and no venous ectasia were more likely to have fistula obliteration following radiosurgery. Commonly used grading scales were not reliable predictors of outcome following radiosurgery.

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## Hemorrhage risk of cerebral dural arteriovenous fistulas following Gamma Knife radiosurgery in a multicenter international consortium

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**Objective:** The authors performed a study to evaluate the hemorrhagic rates of cerebral dural arteriovenous fistulas (dAVFs) and the risk factors of hemorrhage following Gamma Knife radiosurgery (GKRS).

**Methods:** Data from a cohort of patients undergoing GKRS for cerebral dAVFs were compiled from the International Radiosurgery Research Foundation. The annual posttreatment hemorrhage rate was calculated as the number of hemorrhages divided by the patient-years at risk. Risk factors for dAVF hemorrhage prior to GKRS and during the latency period after radiosurgery were evaluated in a multivariate analysis.

**Results:** A total of 147 patients with dAVFs were treated with GKRS. Thirty-six patients (24.5%) presented with hemorrhage. dAVFs that had any cortical venous drainage (CVD) (OR = 3.8,  $p = 0.003$ ) or convexity or torcula location (OR = 3.3,  $p = 0.017$ ) were more likely to present with hemorrhage in multivariate analysis. Half of the patients had prior treatment (49.7%). Post-GKRS hemorrhage occurred in 4 patients, with an overall annual risk of 0.84% during the latency period. The annual risks of post-GKRS hemorrhage for Borden type 2-3 dAVFs and Borden type 2-3 hemorrhagic dAVFs were 1.45% and 0.93%, respectively. No hemorrhage occurred after radiological confirmation of obliteration. Independent predictors of hemorrhage following GKRS included nonhemorrhagic neural deficit presentation (HR = 21.6,  $p = 0.027$ ) and increasing number of past endovascular treatments (HR = 1.81,  $p = 0.036$ ).

**Conclusions:** Patients have similar rates of hemorrhage before and after radiosurgery until obliteration is achieved. dAVFs that have any CVD or are located in the convexity or torcula were more likely to present with hemorrhage. Patients presenting with nonhemorrhagic neural deficits and a history of endovascular treatments had higher risks of post-GKRS hemorrhage.

## Risk of radiation-associated intracranial malignancy after stereotactic radiosurgery: a retrospective, multicentre, cohort study



Amparo Wolf, Kyla Naylor, Moses Tam, Akram Habibi, Josef Novotny, Roman Liščák, Nuria Martinez-Moreno, Roberto Martinez-Alvarez, Nathaniel Sisterson, John G Golfino, Joshua Silverman, Hideyuki Kano, Jason Sheehan, L. Dade Lunsford, Douglas Kondziolka

**Background:** A major concern of patients who have stereotactic radiosurgery is the long-term risk of having a secondary intracranial malignancy or, in the case of patients with benign tumours treated with the technique, the risk of malignant transformation. The incidence of stereotactic radiosurgery-associated intracranial malignancy remains unknown; therefore, our aim was to estimate it in a population-based study to assess the long-term safety of this technique.

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**Methods:** We did a population-based, multicentre, cohort study at five international radiosurgery centres (Na Homolce Hospital, Prague, Czech Republic [n=2655 patients]; Ruber International Hospital, Madrid, Spain [n=1080], University of Pittsburgh Medical Center, Pittsburgh, PA, USA [n=1027]; University of Virginia, Charlottesville, VA, USA [n=80]; and NYU Langone Health System, New York, NY, USA [n=63]). Eligible patients were of any age, and had Gamma Knife radiosurgery for arteriovenous malformation, trigeminal neuralgia, or benign intracranial tumours, which included vestibular or other benign schwannomas, WHO grade 1 meningiomas, pituitary adenomas, and haemangioblastoma. Patients were excluded if they had previously had radiotherapy or did not have a minimum follow-up time of 5 years. The primary objective of the study was to estimate the incidence of stereotactic radiosurgery-associated intracranial malignancy, including malignant transformation of a benign lesion or development of radiation-associated secondary intracranial cancer, defined as within the 2 Gy isodose line. Estimates of age-adjusted incidence of primary CNS malignancies in the USA and European countries were retrieved from the Central Brain Tumor Registry of the United States (CBTRUS) and the International Agency for Research on Cancer (IARC) Global Cancer statistics.

**Findings:** Of 14 168 patients who had Gamma Knife stereotactic radiosurgery between Aug 14, 1987, and Dec 31, 2011, in the five contributing centres, 4905 patients were eligible for the analysis (had a minimum follow-up of 5 years and no history of previous radiation therapy). Diagnostic entities included vestibular schwannomas (1011 [20.6%] of 4905 patients), meningiomas (1490 [30.4%]), arteriovenous malformations (1089 [22.2%]), trigeminal neuralgia (565 [11.5%]), pituitary adenomas (641 [13.1%]), haemangioblastoma (29 [0.6%]), and other schwannomas (80 [1.6%]). With a median follow-up of 8.1 years (IQR 6.0-10.6), two (0.0006%) of 3251 patients with benign tumours were diagnosed with suspected malignant transformation and one (0.0002%) of 4905 patients was considered a case of radiosurgery-associated intracranial malignancy, resulting in an incidence of 6.87 per 100 000 patient-years (95% CI 1.15-22.71) for malignant transformation and 2.26 per 100 000 patient-years (0.11-11.17) for radiosurgery-associated intracranial malignancy. Two (0.0004%) of 4905 patients developed intracranial malignancies, which were judged unrelated to the radiation field. Overall incidence of radiosurgery-associated malignancy was 6.80 per 100 000 patients-years (95% CI 1.73-18.50), or a cumulative incidence of 0.00045% over 10 years (95% CI 0.00-0.0034). The overall incidence of 6.8 per 100 000, after stereotactic radiosurgery was found to be similar to the risk of developing a malignant CNS tumour in the general population of the USA and some European countries as estimated by the CBTRUS and IARC data, respectively.

**Interpretation:** These data show that the estimated risk of an intracranial secondary malignancy or malignant transformation of a benign tumour in patients treated with stereotactic radiosurgery remains low at long-term follow-up, and is similar to the risk of the general population to have a primary CNS tumour. Although prospective cohort studies with longer follow-up are warranted to support the results of this study, the available evidence suggests the long-term safety of stereotactic radiosurgery and could support physicians counselling patients on Gamma Knife stereotactic radiosurgery.

## RESEARCH—HUMAN—CLINICAL STUDIES

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### Stereotactic Radiosurgery for Trigeminal Neuralgia in Patients With Multiple Sclerosis: A Multicenter Study

**BACKGROUND:** Facial pain response (PR) to various surgical interventions in patients with multiple sclerosis (MS)-related trigeminal neuralgia (TN) is much less optimal. No large patient series regarding stereotactic radiosurgery (SRS) has been published.

**OBJECTIVE:** To evaluate the clinical outcomes of MS-related TN treated with SRS.

**METHODS:** This is a retrospective cohort study. A total of 263 patients contributed by 9 member tertiary referral Gamma Knife centers (2 in Canada and 7 in USA) of the Interna-

**Background:** Facial pain response (PR) to various surgical interventions in patients with multiple sclerosis (MS)-related trigeminal neuralgia (TN) is much less optimal. No large patient series regarding stereotactic radiosurgery (SRS) has been published.

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**Objective:** To evaluate the clinical outcomes of MS-related TN treated with SRS. **METHODS:** This is a retrospective cohort study. A total of 263 patients contributed by 9 member tertiary referral Gamma Knife centers (2 in Canada and 7 in USA) of the International Gamma Knife Research Consortium (IGKRF) constituted this study.

**Results:** The median latency period of PR after SRS was 1 mo. Reasonable pain control (Barrow Neurological Institute [BNI] Pain Scores I-IIIb) was achieved in 232 patients (88.2%). The median maintenance period from SRS was 14.1 months (range, 10 days to 10 years). The actuarial reasonable pain control maintenance rates at 1 yr, 2 yr, and 4 yr were 54%, 35%, and 24%, respectively. There was a correlation between the status of achieving BNI-I and the maintenance of facial pain recurrence-free rate. The median recurrence-free rate was 36 mo and 12.2 mo in patients achieving BNI-I and BNI > I, respectively ( $P = .046$ ). Among 210 patients with known status of post-SRS complications, the new-onset of facial numbness (BNI-I or II) after SRS occurred in 21 patients (10%).

**Conclusion:** In this largest series SRS offers a reasonable benefit to risk profile for patients who have exhausted medical management. More favorable initial response to SRS may predict a long-lasting pain control.

## Recently Completed Retrospective Trials

1. Volume-Stage SRS for Large AVMs. PI: Zachary
2. AVM ARE and delayed cyst formation. PI: Kano
3. Gamma Knife SRS in Small Cell Lung Cancer. PI: Cifarelli
4. SRS cavernous malformations. PI: Kano
5. Gamma Ventral Capsulotomy for OCD. PI: Gupta
6. SRS in a distal aneurysm not associated with AVM. PI: Liscak
7. SRS for Trigeminal Schwannoma. PI: Niranjana
8. Small-cell lung cancer brain metastases managed with first-line SRS without prior WBRT or PCI  
Co-PI Rusthoven and Robin

## Current (open) Retrospective Trials

1. Effect of timing of Trigeminal Neuralgia SRS. PI: Kondziolka
2. Central Neurocytoma SRS. PI: Chieh-Hung and Sheehan
3. SRS for meningiomas in NF-2 Patients. PI: Mohammed and Sheehan
4. SRS for Vestibular Schwannoma in NF-2 Patients. PI: Faramand and Niranjana
5. SRS for Choroid Plexus Papilloma. PI: Faramand
6. SRS for Oculomotor nerve (III, IV, VI) schwannomas. PI: Mathieu
7. Radiosurgery for Metastatic Orbital Tumors. PI: Niranjana
8. Outcomes after Vestibular Schwannomas in Neurofibromatosis Type 2. PI: Faramand
9. Primary SRS for Vestibular Schwannomas in Patients with Serviceable Hearing. PI: Kano
10. Radiation dose to neuroanatomic structures of nonfunctioning pituitary adenomas and the effect of SRS on pituitary function. PI: Pomeranec, Sheehan
11. Evaluating the relationship between tumor location and functional outcome after SRS for facial nerve schwannoma. PI: Mehta

## Prospective Clinical Trial

12-02: Multicenter Phase II Study of border zone SR with Bevacizumab chemotherapy in patients with recurrent or progressive glioblastoma multiforme (PI: Dr. Niranjana): Closed, Results uploaded on clinicaltrials.gov.

## IRRF 2018 Research Grant Awards

1. Thalamic Segmentation using Advanced MR Imaging Techniques. PI: Ajay Niranjana
2. An Automated CAD System to Track Brain Metastases on MRI over Time. PI: John YK Lee

## IRRF Membership Update

At present IRRF has 34 active members and 3 Associate members. In the year 2018, following members joined the IRRF.

### New Full Members

1. University of Colorado
2. University of Louisville, House Ear Institute

### New Associate Members

1. Post Graduate Institute of Medical Education & Research (PGIMER), Chandigarh, India
2. National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India

## IRRF Biennial Meeting 2020

The next biennial meeting of IRRF will be held in collaboration with ISRS in New York, Long Island Marriot Hotel (June 18-20, 2020).

## Radiosurgery Center Spotlight

### Gamma Knife Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India

The department of Neurosurgery at PGIMER, Chandigarh has been regarded among the leaders of academic and clinical institutes of India. The radiosurgery services at PGIMER, Chandigarh got a new boost with the installation of Leksell Perfexion machine in 2009. Late Professor Kanchan Kumar Mukherjee was instrumental in bringing the radio surgical services to the global standards. At present, PGIMER is treating nearly 500 patients per year with GKRS for all spectrum of neurosurgical ailments. We have a fully functional GKRS program led by Manjul Tripathi, Manoj K Tewari from Neurosurgery, Narendra Kumar and Renu Madan from Radiation Oncology, and Arun S Oinam from Medical Physics. We are proud member of Leksell Gamma Knife Society, International Radiosurgery Research Foundation, and Radiosurgery section of European Association of Neurological Surgeons. Our research focus is paediatric radiosurgery, dose and volume fractionation of large volume vascular malformations, glomus tumors, and functional radiosurgery for pain, movement disorders, and psychosurgery.

