

IGKRF

International Gamma Knife Research Foundation

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

Fall 2016

In this issue:

Update on IGKRF Activities
The IGKRF
Recently Published Articles
Topics Studied in 2015
New Proposals for 2016
Prospective Clinical Trial Update
IGKRF Member Update
Spotlight: Cairo

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Chairman's Message

Update on IGKRF Activities

This is an excellent time for an update on the activities of the International Gamma knife Research Foundation. Our membership has evolved with an increased number of international participants. Members are continuing to develop clinical trials and many new ones have been approved by the IGKRF Protocol Review Committee. The goals we have set are designed to improve the outcome data and practice of stereotactic radiosurgery using the Leksell Gamma Knife technologies.

The executive committee, composed of Doug Kondziolka, MD, and Jason Sheehan, MD, have done a great job in overseeing the programs of the foundation. Recently, Ajay Niranjani, MD, agreed to serve as a consultant for many day-to-day responsibilities of the foundation, including monitoring of our funding and approved clinical trials. Publications continue on a regular basis, and certainly special credit goes to the team of Dr. Sheehan, who has spearheaded many collaborative studies.

Our next meeting will be in Philadelphia in June of 2017 hosted by the University of Pennsylvania and John Lee, MD. During that meeting the board will meet to determine successor leadership positions of chairman, vice chairman, and secretary-treasurer. We know that several great people will step up to these positions to build our programs even better. Gene Barnett, MD, will serve as chair of the nominating committee of the board.

I hope to see current and future members at the Philadelphia meeting next year. Information is available on our website IGKRF.org. In the mean time, thanks for your continued participation and productivity as we all work to improve the science and study of stereotactic radiosurgery.

L. Dade Lunsford



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.

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IGKRF's headquarters is currently located at University of Pittsburgh Medical Center (UPMC). L. Dade Lunsford, MD, Douglas Kondziolka, MD, and Jason Sheehan, MD, PhD, currently serve as the board members of the executive committee.

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

Recently Published Articles

JNS

CLINICAL ARTICLE

J Neurosurg 122:1479–1489, 2015

Gamma Knife radiosurgery for posterior fossa meningiomas: a multicenter study

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Objective: Posterior fossa meningiomas represent a common yet challenging clinical entity. They are often associated with neurovascular structures and adjacent to the brainstem. Resection can be undertaken for posterior fossa meningiomas, but residual or recurrent tumor is frequent. Stereotactic radiosurgery (SRS) has been used to treat meningiomas, and this study evaluates the outcome of this approach for those located in the posterior fossa.

Methods: At 7 medical centers participating in the North American Gamma Knife Consortium, 675 patients undergoing SRS for a posterior fossa meningioma were identified, and clinical and radiological data were obtained for these cases. Females outnumbered males at a ratio of 3.8 to 1, and the median patient age was 57.6 years (range 12–89 years). Prior resection was performed in 43.3% of the patient sample. The mean tumor volume was 6.5 cm³, and a median margin dose of 13.6 Gy (range 8–40 Gy) was delivered to the tumor.

Results: At a mean follow-up of 60.1 months, tumor control was achieved in 91.2% of cases. Actuarial tumor control was 95%, 92%, and 81% at 3, 5, and 10 years after radiosurgery. Factors predictive of tumor progression included age greater than 65 years (hazard ratio [HR] 2.36, 95% CI 1.30–4.29, $p = 0.005$), prior history of radiotherapy (HR 5.19, 95% CI 1.69–15.94, $p = 0.004$), and increasing tumor volume (HR 1.05, 95% CI 1.01–1.08, $p = 0.005$). Clinical stability or improvement was achieved in 92.3% of patients. Increasing tumor volume (odds ratio [OR] 1.06, 95% CI 1.01–1.10, $p = 0.009$) and clival, petrous, or cerebellopontine angle location as compared with petroclival, tentorial, and foramen magnum location (OR 1.95, 95% CI 1.05–3.65, $p = 0.036$) were predictive of neurological decline after radiosurgery. After radiosurgery, ventriculoperitoneal shunt placement, resection, and radiation therapy were performed in 1.6%, 3.6%, and 1.5%, respectively.

Conclusions: Stereotactic radiosurgery affords a high rate of tumor control and neurological preservation for patients with posterior fossa meningiomas. Those with a smaller tumor volume and no prior radiation therapy were more likely to have a favorable response after radiosurgery. Rarely, additional procedures may be required for hydrocephalus or tumor progression.

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Stereotactic radiosurgery for intracranial hemangioblastomas: a retrospective international outcome study

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Objective: The purpose of this study was to evaluate the role of stereotactic radiosurgery (SRS) in the management of intracranial hemangioblastomas.

Methods: Six participating centers of the North American Gamma Knife Consortium and 13 Japanese Gamma Knife centers identified 186 patients with 517 hemangioblastomas who underwent SRS. Eighty patients had 335 hemangioblastomas associated with von Hippel-Lindau disease (VHL) and 106 patients had 182 sporadic hemangioblastomas. The median target volume was 0.2 cm³ (median diameter 7 mm) in patients with VHL and 0.7 cm³ (median diameter 11 mm) in those with sporadic hemangioblastoma. The median margin dose was 18 Gy in VHL patients and 15 Gy in those with sporadic hemangioblastomas.

Results: At a median of 5 years (range 0.5–18 years) after treatment, 20 patients had died of intracranial disease progression and 9 patients had died of other causes. The overall survival after SRS was 94% at 3 years, 90% at 5 years, and 74% at 10 years. Factors associated with longer survival included younger age, absence of neurological symptoms, fewer tumors, and higher Karnofsky Performance Status. Thirty-three (41%) of the 80 patients with VHL developed new tumors and 17 (16%) of the 106 patients with sporadic hemangioblastoma had recurrences of residual tumor from the original tumor. The 5-year rate of developing a new tumor was 43% for VHL patients, and the 5-year rate of developing a recurrence of residual tumor from the original tumor was 24% for sporadic hemangioblastoma patients. Factors associated with a reduced risk of developing a new tumor or recurrences of residual tumor from the original tumor included younger age, fewer tumors, and sporadic rather than VHL-associated hemangioblastomas. The local tumor control rate for treated tumors was 92% at 3 years, 89% at 5 years, and 79% at 10 years. Factors associated with an improved local tumor control rate included VHL-associated hemangioblastoma, solid tumor, smaller tumor volume, and higher margin dose. Thirteen patients (7%) developed adverse radiation effects (ARE) after SRS, and one of these patients died due to ARE.

Conclusions: When either sporadic or VHL-associated tumors were observed to grow on serial imaging studies, SRS provided tumor control in 79%–92% of tumors.

Gamma Knife radiosurgery for facial nerve schwannomas: a multicenter study

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Objective: Facial nerve schwannomas (FNSs) are rare intracranial tumors, and the optimal management of these tumors remains unclear. Resection can be undertaken, but the tumor's intimate association with the facial nerve makes resection with neurological preservation quite challenging. Stereotactic radiosurgery (SRS) has been used to treat FNSs, and this study evaluates the outcome of this approach.

Methods: At 8 medical centers participating in the North American Gamma Knife Consortium (NAGKC), 42 patients undergoing SRS for an FNS were identified, and clinical and radiographic data were obtained for these cases. Males outnumbered females at a ratio of 1.2:1, and the patients' median age was 48 years (range 11-76 years). Prior resection was performed in 36% of cases. The mean tumor volume was 1.8 cm(3), and a mean margin dose of 12.5 Gy (range 11-15 Gy) was delivered to the tumor.

Results: At a median follow-up of 28 months, tumor control was achieved in 36 (90%) of the 40 patients with reliable radiographic follow-up. Actuarial tumor control was 97%, 97%, 97%, and 90% at 1, 2, 3, and 5 years postradiosurgery. Preoperative facial nerve function was preserved in 38 of 42 patients, with 60% of evaluable patients having House-Brackmann scores of 1 or 2 at last follow-up. Treated patients with a House-Brackmann score of 1 to 3 were more likely to demonstrate this level of facial nerve function at last evaluation (OR 6.09, 95% CI 1.7-22.0, $p = 0.006$). Avoidance of temporary or permanent neurological symptoms was more likely to be achieved in patients who received a tumor margin dose of 12.5 Gy or less (log-rank test, $p = 0.024$) delivered to a tumor of ≤ 1 cm(3) in volume (log-rank test, $p = 0.01$).

Conclusions: Stereotactic radiosurgery resulted in tumor control and neurological preservation in most FNS patients. When the tumor is smaller and the patient exhibits favorable normal facial nerve function, SRS portends a better result. The authors believe that early, upfront SRS may be the treatment of choice for small FNSs, but it is an effective salvage treatment for residual/recurrent tumor that remain or progress after resection.

J Neurooncol (2015) 125:317–324
DOI 10.1007/s11060-015-1911-1



CLINICAL STUDY

Post-radiosurgical edema associated with parasagittal and parafalcine meningiomas: a multicenter study

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Abstract: Stereotactic radiosurgery (SRS) offers a high degree of tumor control for benign meningiomas. However, radiosurgery can occasionally incite edema or exacerbate pre-existing peri-tumoral edema. The current study investigates the incidence, timing, and extent of edema around parasagittal or parafalcine meningiomas following SRS. A retrospective multicenter review was undertaken through participating centers in the International Gamma Knife Research Foundation (previously the North American Gamma Knife Consortium or NAGKC). All included patients had a parafalcine or parasagittal meningioma and a minimum of 6 months follow up. The median follow up was 19.6 months (6-158 months). Extent of new or worsening edema was quantitatively analyzed using volumetric analysis; edema indices were longitudinally computed following radiosurgery. Analysis was performed to identify prognostic factors for new or worsening edema. A cohort of 212 patients comprised of 51.9 % ($n = 110$) females, 40.1 % upfront SRS and 59.9 % underwent adjuvant SRS for post-surgical residual tumor. The median tumor volume at SRS was 5.2 ml. Venous sinus compression or invasion was demonstrated in 25 % ($n = 53$). The median marginal dose was 14 Gy (8-20 Gy). Tumor volume control was determined in 77.4 % ($n = 164$ out of 212 patients). Tumor edema progressed and then regressed in 33 % ($n = 70$), was stable or regressed in 52.8 % ($n = 112$), and progressively worsened in 5.2 % ($n = 11$). Tumor location, tumor volume, venous sinus invasion, margin, and maximal dose were found to be significantly related to post-SRS edema in multivariate analysis. SRS affords a high degree of tumor control for patients with parasagittal or parafalcine meningiomas. Nevertheless, SRS can lead to worsening peritumoral edema in a subset of patients such as those with larger tumors (>10 cc) and venous sinus invasion/compression. Long-term follow up is required to detect and appropriately manage post-SRS edema.

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Skull base chondrosarcoma radiosurgery: report of the North American Gamma Knife Consortium

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Objectives: Stereotactic radiosurgery (SRS) is a potentially important option for patients with skull base chondrosarcomas. The object of this study was to analyze the outcomes of SRS for chondrosarcoma patients who underwent this treatment as a part of multimodality management.

Methods: Seven participating centers of the North American Gamma Knife Consortium (NAG-KC) identified 46 patients who underwent SRS for skull base chondrosarcomas. Thirty-six patients had previously undergone tumor resections and 5 had been treated with fractionated radiation therapy (RT). The median tumor volume was 8.0 cm³ (range 0.9–28.2 cm³), and the median margin dose was 15 Gy (range 10.5–20 Gy). Kaplan-Meier analysis was used to calculate progression-free and overall survival rates.

Results: At a median follow-up of 75 months after SRS, 8 patients were dead. The actuarial overall survival after SRS was 89% at 3 years, 86% at 5 years, and 76% at 10 years. Local tumor progression occurred in 10 patients. The rate of progression-free survival (PFS) after SRS was 88% at 3 years, 85% at 5 years, and 70% at 10 years. Prior RT was significantly associated with shorter PFS. Eight patients required salvage resection, and 3 patients (7%) developed adverse radiation effects. Cranial nerve deficits improved in 22 (56%) of the 39 patients who deficits before SRS. Clinical improvement after SRS was noted in patients with abducens nerve paralysis (61%), oculomotor nerve paralysis (50%), lower cranial nerve dysfunction (50%), optic neuropathy (43%), facial neuropathy (38%), trochlear nerve paralysis (33%), trigeminal neuropathy (12%), and hearing loss (10%).

Conclusions: Stereotactic radiosurgery for skull base chondrosarcomas is an important adjunct option for the treatment of these rare tumors, as part of a team approach that includes initial surgical removal of symptomatic larger tumors.

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 (ARUBA). 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.

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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.

JNS

CLINICAL ARTICLE

Stereotactic radiosurgery for cerebral arteriovenous malformations: evaluation of long-term outcomes in a multicenter cohort

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Objective: In this multicenter study, the authors reviewed the results following Gamma Knife radiosurgery (GKRS) of cerebral arteriovenous malformations (AVMs), determined predictors of outcome, and assessed predictive value of commonly used grading scales based upon this large cohort with long-term follow-up.

Methods: Data from a cohort of 2236 patients undergoing GKRS for cerebral AVMs were compiled from the International Gamma Knife Research Foundation. Favorable outcome was defined as AVM obliteration and no posttreatment hemorrhage or permanent symptomatic radiation-induced complications. Patient and AVM characteristics were assessed to determine predictors of outcome, and commonly used grading scales were assessed.

Results: The mean maximum AVM diameter was 2.3 cm, with a mean volume of 4.3 cm³. A mean margin dose of 20.5 Gy was delivered. Mean follow-up was 7 years (range 1-20 years). Overall obliteration was 64.7%. Post-GRKS hemorrhage occurred in 165 patients (annual risk 1.1%). Radiation-induced imaging changes occurred in 29.2%; 9.7% were symptomatic, and 2.7% had permanent deficits. Favorable outcome was achieved in 60.3% of patients. Patients with prior nidus embolization (OR 2.1, $p < 0.001$), prior AVM hemorrhage (OR 1.3, $p = 0.007$), eloquent location (OR 1.3, $p = 0.029$), higher volume (OR 1.01, $p < 0.001$), lower margin dose (OR 0.9, $p < 0.001$), and more isocenters (OR 1.1, $p = 0.011$) were more likely to have unfavorable outcomes in multivariate analysis. The Spetzler-Martin grade and radiosurgery-based AVM score predicted outcome, but the Virginia Radiosurgery AVM Scale provided the best assessment.

Conclusions: GKRS for cerebral AVMs achieves obliteration and avoids permanent complications in the majority of patients. Patient, AVM, and treatment parameters can be used to predict long-term outcomes following radiosurgery.

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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.

Stereotactic radiosurgery for intracranial hemangiopericytomas: a multicenter study

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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.

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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.

Topics Studied by IGKRF Members in 2015

- Pineal Region Tumors
- Glossopharyngeal Neuralgia
- Hemangiopericytoma
- Falx/convexity Meningioma: Edema after radiosurgery
- Jugular Foramen Schwannoma
- Cavernous Sinus Cavernous Hemangiomas
- TN in Patients with Multiple Sclerosis
- Metastatic Tumors of the Brainstem
- Central Nervous System Lymphoma
- Early Versus Late SRS for Pituitary adenomas

New Proposals Approved for Multicenter Studies in 2016

- Secondary Tumors after SRS
- SRS for Ependymoma
- Radiosurgery for Dural Arteriovenous Fistulas (DAVF)
- Repeat GK for AVMs
- Tremor Radiosurgery
- Volume staged SRS for Large AVMs
- Foramen Magnum Meningioma SRS
- Repeat SRS for Vestibular Schwannomas
- AVM-related Epilepsy
- SRS for Cushing's Disease
- SRS for Acromegaly
- SRS for Pilocytic Astrocytoma
- SRS for Cystic vestibular Schwannoma

Prospective Clinical Trial Update

- 12-01: Randomized controlled study of outcomes in patients with five or more brain metastases (PI: Dr. Barani): Discontinued.
- 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
- 13-01: Radiosurgery or open surgery for epilepsy (ROSE) (PI: Drs. Barbaro/Quigg): Discontinued.

IGKRF Member Update

At present we have 27 active members and four provisional members (listed below).

New Full Members

- NA Homolce Hospital, Czech Republic
- Mayfield Clinic, Jewish Hospital, Cincinnati, Ohio
- Gamma Knife Humanitas Research Hospital, Milan, Italy
- Centro Gamma Knife Dominicano, Santo Domingo, Dominican Republic
- San Diego Gamma Knife Center
- Gamma Knife Center, Nasser Institute, Cairo, Egypt
- Lovelace Gamma Knife Center, Albuquerque, N.M.
- Acibadem Kozyatagi, Turkey

Provisional Members

- RS Unit, Ruber, Madrid
- GK Center, Beijing
- GK Center, West China
- University of Minnesota

Spotlight: Gamma Knife Center, Nasser Institute: Cairo, Egypt

The Gamma Knife Center in Cairo was established in 2001 as a joint venture between Egypt and Sweden. It is a leader in providing top quality radiosurgery treatment and has become a center of excellence in Egypt, the middle east, and Africa. The center has treated more than 5,700 patients and is now using Gamma Knife Perfexion. The center is interested in research and has published 22 articles in peer-reviewed journals and has presented 35 abstracts and lectures in international conferences around the world. A dedicated team of neurosurgeons, oncologists, physicists, and trained nurses are doing their best to provide the best management with expert consultations and follow-up.

