

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

The North American Gamma Knife Consortium Becomes the International Gamma Knife Research Foundation

Since our original organizational meetings in 2008, the need for higher level scientific evidence related to the outcomes of stereotactic radiosurgery (SRS) has continued to mount. Although more than 2000 published articles have established radiosurgery as an important part of the world of current neurosurgery and radiation oncology, government and private health insurance, patients and referring doctors continue to question where and when radiosurgery becomes an important option. Our original 11 affiliated medical centers has steadily grown to include 20 North American Centers, two European centers, and four Asian centers. As a result of the expansion to international membership, the Board decided to move forward with a new name and revised bylaws. As before the full board consists of a designated representative from each center. The executive committee includes the Chair, Vice Chairman, and Secretary-Treasurer. The IGKRF is a US 501 3-C tax exempt organization.

The purpose of the organization was to improve the quantity and quality of knowledge related to the role of stereotactic radiosurgery using a common technology, the Leksell Gamma Knife®. During the initial seven years the organization has performed 12 multicenter retrospective trials and all have been published. Prospective trials include 12-01, which evaluated neurocognitive outcomes in patients with five or more brain metastases. 12-02 evaluates the outcomes of border zone SRS plus bevacizumab for progressive glioblastoma. NAGKC 13-01 (the ROSE trial) will fund the final patients selected for epilepsy radiosurgery. Contractual funding for these prospective trials was underwritten by grants from the foundation and industry (AB Elekta and Genentech). The protocol review committee headed by Manmeet Ahluwalia is evaluating newly proposed studies.

In 2015 our expanding role prompted the conversion of the consortium to the International Gamma Knife Research Foundation (IGKRF), an entity more reflective of the goals, our legal organization, and our funding sources. Currently, more than 18 retrospective clinical trials are in process and four additional prospective clinical trials are under evaluation. The IGKRF has continued to explore new fund raising mechanisms including additional industry sources and individual donations. Dedicated space and full time employees are needed to expand the efforts of the foundation over the next five years. In line with a goal to maintain a low overhead, we continue to rely on services provided by foundation board and their staffs.

As we continue to grow the challenges will grow, especially the need for dedicated infrastructure, research coordinators, an executive director, and most importantly, additional fund raising efforts. For international membership initiation fees and annual dues are difficult to get funded.

We encourage members to get involved in the committees, to propose clinical trials, to pursue potential funding sources, and consider designated donations to support the scientific goals of the IGKRF. I look forward to seeing many of you at the next scientific meeting in Cleveland in June. I want to especially thank Gene Barnett and Jason Sheehan for their organizational efforts for this meeting.

See you in Cleveland!

L. Dade Lunsford



Recently Published Articles

Gamma Knife Radiosurgery for Cerebellopontine Angle Meningiomas: A Multicenter Study

Ding D, Starke RM, Kano H, Nakaji P, Barnett GH, Mathieu D, Chiang V, Omay SB, Hess J, McBride HL, Honea N, Lee JYK, Rahmathulla G, Evanoff WA, Alonso-Basanta M, Lunsford LD, Sheehan JP. *Neurosurgery* 75(4):398-408, 2014.

Background: Resection of cerebellopontine angle (CPA) meningiomas may result in significant neurological morbidity. Radiosurgery offers a minimally invasive alternative to surgery.

Objective: To evaluate, in a multicenter cohort study, the outcomes of patients harboring CPA meningiomas who underwent Gamma Knife radiosurgery (GKRS).

Methods: From 7 institutions participating in the North American Gamma Knife Consortium, 177 patients with benign CPA meningiomas treated with GKRS and at least 6 months radiologic follow-up were included for analysis. The mean age was 59 years and 84% were female. Dizziness or imbalance (48%) and cranial nerve (CN) VIII dysfunction (45%) were the most common presenting symptoms. The median tumor volume and prescription dose were 3.6 cc and 13 Gy, respectively. The mean radiologic and clinical follow-up durations were 47 and 46 months, respectively. Multivariate regression analyses were performed to identify the predictors of tumor progression and neurological deterioration.

Results: The actuarial rates of progression-free survival at 5 and 10 years were 93% and 77%, respectively. Male sex ($P = .014$), prior fractionated radiation therapy ($P = .010$), and ataxia at presentation ($P = .002$) were independent predictors of tumor progression. Symptomatic adverse radiation effects and permanent neurological deterioration were observed in 1.1% and 9% of patients, respectively. Facial spasms at presentation ($P = .007$) and lower maximal dose ($P = .011$) were independently associated with neurological deterioration.

Conclusions: GKRS is an effective therapy for CPA meningiomas. Depending on the patient and tumor characteristics, radiosurgery can be an adjuvant treatment to initial surgical resection or a standalone procedure that obviates the need for resection in most patients.

Radiosurgery is an Effective Treatment for Recurrent Esthesioneuroblastoma: A Multicenter Study.

Van Gompel JJ, Link MJ, Sheehan JP, Xu Z, Mathieu D, Kano H, Lunsford LD. *J Neurol Surg B Skull Base* 75(6):409-14, 2014.

Objective: Esthesioneuroblastoma (ENB) is a rare malignant neuroendocrine neoplasm that is prone to both local and metastatic recurrence. Local recurrence may often be treated with repeat resection. However, stereotactic radiosurgery (SRS) offers a noninvasive option.

Participants: Gamma knife prospective databases were queried at all institutions within the North American Gamma Knife Consortium, 16 at the time of this report. All patients who had undergone SRS for ENB were included. Main Outcome Measure Response of recurrent ENB to SRS.

Results: A total of 31 locally recurrent tumors in 13 patients were treated with SRS. The median age was 49 years (range: 19-79 years). At a median follow-up of 36 months (range: 1-100 months), 13 (48%) treated tumors were smaller, 11 (41%) were stable, and 3 (11%) showed continued growth following SRS. Univariate analysis did not find any significant factor relating to failure of treatment. Notably, no treatment-related complications (0%) were observed in this cohort.

Conclusions: SRS appears to provide a safe and effective option for treatment of recurrent intracranial ENB. Overall, 89% of treated tumors were controlled in this multi-institutional study.

The Results of a Third Gamma Knife Procedure for Recurrent Trigeminal Neuralgia.

Tempel ZJ, Chivukula S, Monaco EA 3rd, Bowden G, Kano H, Niranjana A, Chang EF, Sneed PK, Kaufmann AM, Sheehan J, Mathieu D, Lunsford LD. *J Neurosurg* 122(1):169-79, 2015.

Object: Gamma Knife radiosurgery (GKRS) is the least invasive treatment option for medically refractory, intractable trigeminal neuralgia (TN) and is especially valuable for treating elderly, infirm patients or those on anticoagulation therapy. The authors reviewed pain outcomes and complications in TN patients who required 3 radiosurgical procedures for recurrent or persistent pain.

Methods: A retrospective review of all patients who underwent 3 GKRS procedures for TN at 4 participating centers of the North American Gamma Knife Consortium from 1995 to 2012 was performed.

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The Barrow Neurological Institute (BNI) pain score was used to evaluate pain outcomes.

Results: Seventeen patients were identified; 7 were male and 10 were female. The mean age at the time of last GKRS was 79.6 years (range 51.2-95.6 years). The TN was Type I in 16 patients and Type II in 1 patient. No patient suffered from multiple sclerosis. Eight patients (47.1%) reported initial complete pain relief (BNI Score I) following their third GKRS and 8 others (47.1%) experienced at least partial relief (BNI Scores II-IIIb). The average time to initial response was 2.9 months following the third GKRS. Although 3 patients (17.6%) developed new facial sensory dysfunction following primary GKRS and 2 patients (11.8%) experienced new or worsening sensory disturbance following the second GKRS, no patient sustained additional sensory disturbances after the third procedure. At a mean follow-up of 22.9 months following the third GKRS, 6 patients (35.3%) reported continued Score I complete pain relief, while 7 others (41.2%) reported pain improvement (BNI Scores II-IIIb). Four patients (23.5%) suffered recurrent TN following the third procedure at a mean interval of 19.1 months.

Conclusions: A third GKRS resulted in pain reduction with a low risk of additional complications in most patients with medically refractory and recurrent, intractable TN. In patients unsuitable for other microsurgical or percutaneous strategies, especially those receiving long-term oral anticoagulation or antiplatelet agents, GKRS repeated for a third time was a satisfactory, low risk option.

Stereotactic Radiosurgery for Intracranial Hemangioblastomas: A Retrospective International Outcome Study.

Kano H, Shuto T, Iwai Y, Sheehan J, Yamamoto M, McBride HL, Sato M7, Serizawa T, Yomo S, Moriki A, Kohda Y, Young B, Suzuki S, Kenai H, Duma C, Kikuchi Y, Mathieu D, Akabane A, Nagano O, Kondziolka D, Lunsford LD. *J Neurosurg* 122(6):1469-78, 2015

Object: 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 cm(3) (median diameter 7 mm) in patients with VHL and 0.7 cm(3) (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 Posterior Fossa Meningiomas: A Multicenter Study.

Sheehan JP, Starke RM, Kano H, Barnett GH, Mathieu D, Chiang V, Yu JB, Hess J, McBride HL, Honea N, Nakaji P, Lee JY, Rahmathulla G, Evanoff WA, Alonso-Basanta M, Lunsford LD. *J Neurosurg* 122(6):1479-89, 2015.

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 under-

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taken 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.

Gamma Knife Radiosurgery for Facial Nerve Schwannomas: A Multicenter Study.

Sheehan JP, Kano H, Xu Z, Chiang V, Mathieu D, Chao S, Akpınar B, Lee JY, Yu JB, Hess J, Wu HM, Chung WY, Pierce J, Missios S, Kondziolka D, Alonso-Basanta M, Barnett GH, Lunsford LD. *J Neurosurg* 8:1-8, 2015.

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 cm³, 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 available 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 cm³ 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.

Retrospective Trials In Progress

- Craniopharyngioma, (Niranjan/UPMC)
- AVM radiosurgery grading scale, (Sheehan/ UVA)
- Pineal region tumors, (Kano/UPMC & Mathieu/U. Sherbrooke)
- CS hemangioma, (Lee/Taipei & Sheehan/ UVA)
- Repeat SRS for AVMs, (Kano/UPMC)
- Glossopharyngeal neuralgia, (Kano/UPMC)
- Hemangiopericytoma, (Sheehan/ UVA)
- Falx/convexity meningioma edema, (Sheehan/ UVA)
- Jugular Foramen Schwannomas, (Kano/UPMC & Meola/UPMC)
- MS-related Trigeminal neuralgia, (Xu/UVA)
- Orbital Hemangioma, (Wu/Taipei)

New Proposals

- Brainstem Metastasis, (Trifiletti/UVA)
- Pleomorphic xanthoastrocytoma, (Kano/UPMC)
- Hypothalamic Hamartoma, (Kano/UPMC)
- Non Functioning Pituitary adenoma early vs. delayed surgery, (Pomeranec/UVA)
- Trigeminal schwannoma, (Niranjan/UPMC)

Ongoing Prospective Clinical Trials

- 12-01: Randomized controlled study of outcomes in patients with five or more brain metastases (PI: Dr. Barani): Approximately 20 patients have been accrued at UCSF thus far. Yale has recently had its site visit. Other site visits are imminent.
- 12-02: Multicenter Phase II Study of border zone SR with Bevacizumab chemotherapy in patients with recurrent or progressive glioblastoma multiforme (PI: Dr. Niranjan): University of Pittsburgh is in the process of signing a contract with Genentech. The target accrual is 40 patients. Dr. Niranjan will draft a multicenter protocol to broaden the patient accrual at other member centers.
- 13-01: Radiosurgery or open surgery for epilepsy (ROSE) (PI: Drs. Barbaro/Quigg): The ROSE trial contract is working its way through the administrative process at UVA. The study will hopefully accrue a smaller number of patients. Patients could be accrued through other countries including England and India.

Potential Prospective Clinical Trials

- 13-02: Staged stereotactic radiosurgery followed by embolization for large volume AVMs (PI: Dr. Kano)
- 14-01: Minocycline for ARE in brain metastasis (PI: Dr. Niranjan)
- A Phase I trial of Afatinib for SRS brain mets for patients with HER2 positive breast cancer and EGFR positive lung cancer with 1-4 brain metastases (Dr. Ahulwalia)

New IGKRF Members

The Valley Hospital, GK Center
RS Unit, Ruber International Hospital, Madrid Spain

NA Homolce Hospital, Czech Republic
GK Center of Beijing Neurosurgical Institute

Tian Tan Hospital of Capital Medical University
Gamma Knife Center of West China Hospital

Upcoming Scientific Conference: Cleveland 2015 'Going Global'

The Second Scientific Conference of the International Gamma Knife Research Foundation will be held in Cleveland, Ohio, on June 26-28. Sponsored by the Cleveland Clinic, the conference will bring together radiosurgery professionals from around the world to discuss research and clinical topics relative to the Leksell Gamma Knife.

Events for the conference will be held at the Cleveland Public Library. The host hotel for the conference is the Hyatt Regency Cleveland Hotel at the Arcade, located at 420 East Superior Avenue, directly across the street.

A Gamma Knife Perfexion upgrade course will also be offered during the conference at the Cleveland Clinic Gamma Knife Center.

For more information on the conference, to learn how to register, or to download the conference brochure, please visit the conference web page on the International Gamma Knife Research Foundation website at igkrf.org/cleveland2015.



Spotlight: Taipei Veterans General Hospital

Taipei Veterans General Hospital installed the first Gamma Knife machine in Taiwan in 1993. Dr. Hung-Chi Pan and Dr. Wan-Yuo Guo then set up the first Gamma Knife team in the hospital. Since then their Gamma Knife center has treated more than 6,000 cases and about 300-400 patients per year. The Taipei team has accumulated treatment experience in various indications and has continued to publish results especially in the treatment of vascular disorders such as large arterio-venous malformation and dural arterio-venous fistulae. In November of 2013, the Taipei center upgraded their machine to Gamma Knife Perfexion and have continued to provide high quality radiosurgery treatment in Taiwan.



Taipei Veterans General Hospital
Gamma Knife Center staff.