Gamma Knife Radiosurgery
Clinical Indications in Selected References

Bodo Lippitz
Medinstructor
Content

Introduction .................................................................................................................................................. 3

1. Gamma Knife Treatment Indications: Overview .................................................................................. 4

  1.a. Technical Accuracy ............................................................................................................................. 5

  1.b. Radiation Conformity .......................................................................................................................... 6

Gamma Knife Radiosurgery: Clinical Efficacy ......................................................................................... 8

2. Brain Metastases ........................................................................................................................................ 8

  2.a. Brain Metastases from Breast Cancer ............................................................................................... 8

    Selected Literature 1998-2012: Gamma Knife in the Treatment of Brain Metastases from Breast Cancer) 9

  2.b. Brain Metastases from Lung Cancer ................................................................................................. 26

    Selected Literature 2002-2012: Brain Metastases from Lung cancer ...................................................... 27

  2.c. Brain Metastases from Renal Cancer ............................................................................................... 43

    Selected Literature 1997-2011: Brain Metastases from Renal Cancer .................................................... 43

  2.d. Brain Metastases from Malignant Melanoma .................................................................................... 53

    Selected Literature 1998-2011: Brain Metastases from Malignant Melanoma ........................................ 53

  2.e. Brain Metastases from Colo-rectal Carcinoma .................................................................................. 72

    Selected Literature 2002-2012: Brain Metastases from Colo-rectal Carcinoma ....................................... 72

    Selected Literature: Quality of Life and Treatment of Brain Metastases ................................................. 80

    Abstracts of cited references: Gamma Knife in the Treatment of Multiple Brain Metastases .................. 88

3. Meningiomas ........................................................................................................................................... 103

    Selected Literature 1999-2012 : Gamma Knife Radiosurgery for Meningioma .................................... 103

4. Acoustic Neuroma .................................................................................................................................. 130

    Selected Literature 2000-2011: Gamma Knife Radiosurgery for Vestibular Schwannoma .................. 131

5. Pituitary adenomas ............................................................................................................................... 157

    Selected Literature 1998-2012: Gamma Knife Radiosurgery for Pituitary Adenoma (Acromegaly) ....... 157

    Selected Literature 2000-2010: Gamma Knife Radiosurgery for Pituitary Adenoma (Cushing’s disease) ... 178

    Selected Literature 2003-2011: Gamma Knife Radiosurgery for (non-secreting) Pituitary Adenoma ........ 187

6. Gamma Knife Radiosurgery for glioma ............................................................................................... 200

    Selected Literature 1996-2011: Gamma Knife Radiosurgery for Glioma ............................................. 201

7. Arterio-venous malformations (AVM) ................................................................................................. 226

    Selected Literature 2001-2012: Gamma Knife Radiosurgery for Arterio-Venous Malformations (AVM) .... 226


    Selected Literature 1996-2012: Gamma Knife Thalamotomy for Movement Disorders (and other functional indications) ........................................................................................................... 260

9. Trigeminal neuralgia ............................................................................................................................. 279

    Selected Literature 2001-2012: Gamma Knife Radiosurgery for Trigeminal neuralgia ......................... 280
Introduction

The principle of Gamma Knife radiosurgery implies concentrating radiation within a target in the brain while avoiding radiation of the surrounding healthy tissue. Leksell Gamma Knife achieves this by the mechanical focusing of ca. 192 radiation sources, which allows shaping of an extremely defined irradiated volume in the brain. With modern planning techniques and multiple isocenters, virtually any shape of tumor can be matched with high-precision radiation. Radiosurgical techniques (and particularly Gamma Knife radiosurgery) provide a very steep radiation dose fall-off. The irradiation hits the pathological cells with a locally high concentration of energy, while at the same time the neighboring areas of the brain are spared from being affected by the irradiation. This specific gradient of radiation in all three dimensions guarantees that the surrounding brain tissue is exposed to only very little radiation and is thereby “protected” against undesired radiation effects.

Radiosurgery is generally carried out in one session under local anesthesia, resulting in very low physical stress for the patient. The necessary precision of target localization requires a stereotactic MRI or CT study before radiosurgery and a stereotactic frame fixation (for Linac and Gamma Knife). Radiation doses are expressed as “prescription doses” or “minimum doses” reflecting the dose applied to the tumor periphery. Generally, prescription doses of 15–25 Gy are applied in radiosurgery of brain tumors. In Gamma Knife treatments this minimum dose commonly corresponds to 50% of the maximally applied dose (50% isodose), resulting in an inhomogeneous dose distribution within the tumor often in the range 36–50 Gy. The lack of dose homogeneity is irrelevant for the outcome, because the high-dose area lies within the tumor tissue.

The stereotactic head frame guarantees the precision needed to protect healthy brain tissue and directs the radiation focus to the target. So far about 600,000 patients have been treated with 249 Gamma Knifes worldwide. The number of patients treated annually has doubled in the last decade and is increasing steadily.
1. Gamma Knife Treatment Indications: Overview

The Gamma Knife technology has enabled neurosurgeons to treat many conditions that are otherwise inaccessible to therapy. The goal of radiosurgery is to maintain quality of life.

In some indications Gamma Knife replaces the open tumor operation. This comprises either tumors that are surgically inaccessible or tumors that have been treated unsuccessfully by conventional surgery, chemotherapy and/or radiation therapy. In other indications Gamma Knife is used as an additive therapy, which enables the conventional surgeon to operate less radically and thereby with a lower complication rate.

It is important to note that Gamma Knife radiosurgery is highly effective even for tumors that are relatively resistant to traditional external beam radiation therapy. Numerous scientific studies have documented the efficacy of radiosurgery against various brain tumors. The majority of brain metastases can be treated successfully using the Gamma Knife with excellent tumor control rates and low associated morbidity. The method has been shown to be highly effective even against multiple metastases. Recent results even show a beneficial effect of Gamma Knife treatment in the therapy of glioma and pediatric and rare brain tumors such as pilocytic astrocytoma and ependymoma.

Gamma Knife radiosurgery stops the growth of benign brain tumors such as meningioma. In this indication it is generally used as a complement to open neurosurgical resection in order to allow less invasive operations, thereby reducing the otherwise high rate of surgery-related morbidity, intensive care and other ancillary treatments.

A further important group treated with Gamma Knife is patients with vestibular schwannoma (acoustic neurinoma), another benign tumor located close to the brain stem. These patients are otherwise treated with highly sophisticated and invasive open surgery. Radiosurgery provides highly efficient local control of these tumors, avoiding many of the complications that are associated with open surgery.

Gamma Knife treatments have a very long track record in the treatment of postoperatively recurring endocrinologically active as well as inactive pituitary adenoma.

In patients with arteriovenous malformations (AVM) of the brain, Gamma Knife is used as an alternative to open surgery.

Recent results have shown that Gamma Knife radiosurgery is an excellent treatment option for patients with trigeminal neuralgia who fail to respond to medical therapy.
Gamma Knife provides a highly efficient and cost-effective alternative in the treatment of Parkinsonian tremor, which is otherwise treated with highly costly deep brain stimulation.

Summary Treatment Indications

- Brain Metastases
- Vestibular Schwannoma (Acoustic Neurinoma)
- Meningioma
- Glioma and other rare brain tumors
- Pituitary Adenoma
- Arteriovenous Malformations (AVM)
- Trigeminal Neuralgia
- Functional Indications (Thalamotomy for tremor etc.)

1.a. Technical Accuracy

In the recent Gamma Knife model (Perfexion) the accuracy of the mechanical versus radiation isocenter is 0.05 mm (Lindquist 2007). Including the geometrical error from implementation of imaging data, the total error in the Gamma Knife system has been calculated to be 0.48 mm + 0.23 mm (Mack 2002). In comparison, for the CyberKnife, the ideal dynamic alignment margins that accommodate for detection and correction precision have recently been calculated to be 1.5 mm (Murphy 2009). However, since the patient is not frame-fixated during the Cyberknife treatment, the accuracy of the treatment depends on the frequency of x-ray based position control measurements, which are necessary to compensate for the patient’s involuntary movements. In a frame-based technique such as Gamma Knife or Linac, precision is easier to determine using phantoms since patient movements are mechanically avoided.

References Technical Accuracy


1.b. Radiation Conformity

Radiosurgery strictly avoids the radiation of healthy tissues. The closer the prescription dose matches the treated target and the steeper the dose gradient around the irradiated target, the smaller the amount of normal tissue that is irradiated. This dose gradient for a 3-dimensional target is generally quantified using the conformity index, which reflects the amount of normal tissue within the prescription isodose. A simplified conformity index is the ratio of prescription volume to target volume, which would ideally be 1 if no healthy tissue were irradiated. Analysis of 1338 targets treated with previous Gamma Knife systems (1993–1998) showed conformity indices of 1.40–1.43 (Nakamura 2001). The conformity achieved in the most recent Gamma Knife models (Perfexion) is generally higher and polymer gel measurements have verified the planned dose distribution of a Gamma Knife treatment with a conformity of 1.17 (Papagiannis 2005). For stereotactic Linac radiosurgery, this conformity index has been reported to range from 2.7 (Nedzi 1993) to 1.8 for micromultileaf collimator (Kubo 1999).

Gamma Knife plans demonstrated a statistically significantly better conformity when directly compared with fixed-field linear accelerator techniques (Perks 2005). In general, these plans were more successful at conforming to highly irregular shapes than conventional Linac plans (Verhey 1998). In Gamma Knife treatments doses outside the treatment area are very small and generally considered negligible. In comparison, CyberKnife doses within the healthy tissue outside the radiation field were two to five times larger than those measured for the comparable Gamma Knife (Petti 2006).

Extracranial doses vary depending on the technology used. Due to intense shielding, Gamma Knife doses decreased steeply with distance from the treated brain, delivering only 13 mSv at the lower pelvis, in comparison to 117 and 132 mSv during CyberKnife treatments (Zytkovicz 2007). A further reduction of extracranial doses has been shown in the recent Gamma Knife model Perfexion (Regis 2009).

Due to its isocentric planning structure, it is easy for a Gamma Knife to treat many targets such as multiple brain metastases in a single session, which is technically significantly more challenging for alternative techniques such as Linac and Cyberknife.

In conclusion, the geometrical accuracy, dose accuracy and the dose gradient around the target and the protection of extracranial tissue seem to be superior with the Gamma Knife, although reported clinical results after Linac or Cyberknife treatment of brain metastases do not reflect these technical differences. The various technologies achieve similar clinical results. So far there are no comparative studies.
References Radiation Conformity


When compared to other radiosurgical techniques, Gamma Knife is superior in

- 3-dimensional radiation precision
- clinical track record
- number of treated patients
- number of peer-reviewed studies
- number of published long-term studies
Gamma Knife Radiosurgery: Clinical Efficacy

2. Brain Metastases

More than 185,000 treatments for brain metastases have so far been carried out with Gamma Knife radiosurgery. A wide range of retrospective and a few prospective radiosurgical studies with more than 4,800 patients with brain metastases provide consistent and reproducible results with an average local tumor control of between 84% and 97%. Multivariate analysis indicate that longer freedom from progression is significantly associated with a higher radiosurgical dose, local tumor control being superior for metastases treated at minimum doses of 18 Gy or higher. Brain metastases tend to shrink gradually after radiosurgery, the tumor-associated perifocal edema disappearing after several weeks. Stereotactic radiosurgery is effective even against brain metastases from melanoma or renal cancer that are resistant to fractionated external beam radiation. The tumor volume is the most important limiting factor in radiosurgery. The volume of the irradiated healthy brain in the penumbra of the metastasis increases when large metastases are treated. This can result in the formation of a local edema around the irradiated target, typically 6–9 months after radiosurgery. This effect is generally transient, but may require a steroid medication. Adverse radiation effects are generally seen in large metastases or nonconformal treatments and are very rare when metastases smaller than 2.5 cm are treated.

2.a. Brain Metastases from Breast Cancer

Gamma Knife treatment of breast cancer metastases is highly effective, whereas the previously often applied fractionated whole brain radiotherapy only achieved very limited local control, with intracranial failure after a median of 3–5 months (Bartsch 2006, Ogura 2003). In the frequent event of tumor recurrence after fractionated whole brain radiotherapy, Gamma Knife can be used as a highly effective "salvage treatment" of the recurrent brain metastases.

Chemotherapy of breast cancer has made dramatic improvements over the last decade, resulting in significantly prolonged patient survival, unfortunately with no impact on brain metastases. A correspondingly effective treatment of brain metastases from breast cancer is paramount[BT6], but the standard fractionated whole brain radiotherapy has to be considered insufficient to allow reliable control
over brain metastases. Optimization of systemic therapeutic approaches for breast cancer patients emphasizes the necessity for an equally effective radiosurgical treatment of the brain metastases.

Three retrospective analyses after Gamma Knife treatment of breast cancer metastases in a total of 249 patients reported high local tumor control rates of between 93 and 94% (Amendola 2000, Firlik 2000, Muacevic 2004). Interestingly, survival was found to be independent of the number of metastases treated (Amendola 2000). The prognosis of patients with brain metastases of breast cancer seems to be slightly superior when compared to other groups of cancer patients, with a median survival of between 10 and 13 months. Patients in RPA classes I, II and III survived for 34.9, 9.1 and 7.9 months, respectively (Muacevic 2004).

References (Gamma Knife in the Treatment of Brain Metastases from Breast Cancer)


Selected Literature 1998-2012: Gamma Knife in the Treatment of Brain Metastases from Breast Cancer)


Gamma Knife radiosurgery of brain metastasis from breast cancer.

Padovani L, Muracciole X, Régis J.

Radiotherapy Department, Aix-Marseille University, CHU La Timone, Assistance Publique, Hôpitaux de Marseille, Marseille, France.

Abstract

The incidence of brain metastasis in patients with metastatic breast cancer ranges from 14 to 16%. Age, number of metastatic sites, short disease-free survival and molecular subtypes are associated with the occurrence of brain metastasis. Patients classified in the triple-negative group more frequently
presented brain metastasis as the first site (26%) than those in the human epidermal growth factor receptor 2 (HER2)-positive (6%) or luminal (12%) subtypes. Whole brain radiation therapy (WBRT) is still the standard treatment for breast cancer patients with brain metastasis. The 1- and 2-year survival rates of patients with brain metastasis were 25 and 10%, respectively, with a median survival of 6 months. In selected patients with single brain metastasis, majority of lung cancer, three randomized controlled trials underlined the significant survival benefit in adding local treatment such as surgery or stereotactic radio surgery to WBRT. Similarly, the upfront stereotactic radiosurgery (SRS) alone did not affect survival rate in three other randomized studies and represents an alternative treatment for patients with stage 1-4. Metastatic breast cancer patients with Karnofsky Performance Scale ≥70, single or oligometastatic brain metastases and well-controlled extracranial disease or favorable disease-specific graded prognostic assessment group presented a median overall survival of 16 months. Delaying WBRT could spare patients of neurocognitive toxicity due to full-dose whole brain irradiation. Nevertheless, the real WBRT neurocognitive impact is still unclear. These patients should be followed with serial magnetic resonance image every 3 months and treated with WBRT or additional SRS at recurrence to control brain disease.

Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases.

University of Minnesota Gamma Knife, Minneapolis Radiation Oncology, MN, USA.
p sperduto@mropa.com

PURPOSE:
Our group has previously published the Graded Prognostic Assessment (GPA), a prognostic index for patients with brain metastases. Updates have been published with refinements to create diagnosis-specific Graded Prognostic Assessment indices. The purpose of this report is to present the updated diagnosis-specific GPA indices in a single, unified, user-friendly report to allow ease of access and use by treating physicians.

METHODS:
A multi-institutional retrospective (1985 to 2007) database of 3,940 patients with newly diagnosed brain metastases underwent univariate and multivariate analyses of prognostic factors associated with outcomes by primary site and treatment. Significant prognostic factors were used to define the diagnosis-specific GPA prognostic indices. A GPA of 4.0 correlates with the best prognosis, whereas a GPA of 0.0 corresponds to the worst prognosis.
RESULTS:
Significant prognostic factors varied by diagnosis. For lung cancer, prognostic factors were Karnofsky performance score, age, presence of extracranial metastases, and number of brain metastases, confirming the original Lung-GPA. For melanoma and renal cell cancer, prognostic factors were Karnofsky performance score and the number of brain metastases. For breast cancer, prognostic factors were tumor subtype, Karnofsky performance score, and age. For GI cancer, the only prognostic factor was the Karnofsky performance score. The median survival times by GPA score and diagnosis were determined.

CONCLUSION:
Prognostic factors for patients with brain metastases vary by diagnosis, and for each diagnosis, a robust separation into different GPA scores was discerned, implying considerable heterogeneity in outcome, even within a single tumor type. In summary, these indices and related worksheet provide an accurate and facile diagnosis-specific tool to estimate survival, potentially select appropriate treatment, and stratify clinical trials for patients with brain metastases.

Prognostic factors for survival in patients treated with stereotactic radiosurgery for recurrent brain metastases after prior whole brain radiotherapy.
Caballero JA, Sneed PK, Lamborn KR, Ma L, Denduluri S, Nakamura JL, Barani IJ, McDermott MW.
Stanford University School of Medicine, Stanford, CA.

PURPOSE:
To evaluate prognostic factors for survival after stereotactic radiosurgery (SRS) for new, progressive or recurrent brain metastases (BM) after prior whole brain radiotherapy (WBRT).

METHODS AND MATERIALS:
Patients treated between 1991 and 2007 with Gamma Knife SRS for BM after prior WBRT were retrospectively reviewed. Potential prognostic factors were analyzed overall and by primary site using univariate and stepwise multivariate analyses and recursive partitioning analysis, including age, Karnofsky performance status (KPS), primary tumor control, extracranial metastases, number of BM treated, total SRS target volume, and interval from WBRT to SRS.

RESULTS:
A total of 310 patients were analyzed, including 90 breast, 113 non-small-cell lung, 31 small-cell lung, 42 melanoma, and 34 miscellaneous patients. The median age was 56, KPS 80, number of BM treated
3, and interval from WBRT to SRS 8.1 months; 76% had controlled primary tumor and 60% had extracranial metastases. The median survival was 8.4 months overall and 12.0 vs. 7.9 months for single vs. multiple BM treated (p = 0.001). There was no relationship between number of BM and survival after excluding single-BM patients. On multivariate analysis, favorable prognostic factors included age <50, smaller total target volume, and longer interval from WBRT to SRS in breast cancer patients; smaller number of BM, KPS >60, and controlled primary in non-small-cell lung cancer patients; and smaller total target volume in melanoma patients.

CONCLUSIONS:
Among patients treated with salvage SRS for BM after prior WBRT, prognostic factors appeared to vary by primary site. Although survival time was significantly longer for patients with a single BM, the median survival time of 7.9 months for patients with multiple BM seems sufficiently long for salvage SRS to appear to be worthwhile, and no evidence was found to support the use of a cutoff for number of BM appropriate for salvage SRS.

Clinical outcome of central nervous system metastases from breast cancer: differences in survival depending on systemic treatment.

Department of Internal Medicine, Seoul National University College of Medicine, 28 Yongon-Dong, Chongno-Gu, Seoul 110-744, Korea.

Central nerve system (CNS) metastases are a feared complication of breast cancer and are associated with poor prognosis. The purpose of this study is to investigate the clinical characteristics of CNS metastases and to clarify the prognostic factors after CNS metastases in breast cancer at a single institution over a long time period. We retrospectively reviewed the medical records of breast cancer patients diagnosed at Seoul National University Hospital from 1981 to 2009 and identified the patients who experienced CNS metastases. We collected the data, including demographics, clinico-pathologic characteristics, dates of diagnosis of original breast cancer and subsequent metastases, and date of death, and correlated the findings with the clinical outcome. A total of 400 patients were identified, of whom 17 (4.3%) were diagnosed with CNS metastases and primary breast cancer concurrently and 383 (95.7%) experienced CNS metastases subsequent to the diagnosis of primary breast cancer. Further, 318 patients (79.5%) had only brain parenchymal metastases, 30 (7.5%) had only leptomeningeal metastases, and 52 (13%) had both. After the diagnosis of CNS metastasis, 170 patients (42.5%) received systemic chemotherapy (CTx) and 143 (35.8%) received CTx after whole brain radiation therapy (WBRT). The patients with good performance status (PS), initial CNS metastasis as recurrence, absence of extracranial metastases, non-visceral extracranial metastases, longer interval from the date
of primary breast cancer to the date of CNS metastasis, and CTx after WBRT and gamma-knife surgery (GKS), had better outcomes in univariate analyses. In multivariate analysis, good PS, systemic CTx after WBRT, GKS, and longer interval to CNS metastasis, were independent prognostic factors for overall survival after CNS metastases. Our results suggest that appropriate palliative systemic therapy after WBRT or GKS, and adequate palliative treatment via combined modalities are helpful for breast cancer patients, even after the detection of CNS metastases.


Department of Radiation Oncology, Dana-Farber/Brigham and Women's Cancer Center, Boston, Massachusetts; Harvard Medical School, Boston, Massachusetts. paulj.kelly@hse.ie.

BACKGROUND:
Salvage stereotactic radiosurgery (SRS) is often considered in breast cancer patients previously treated for brain metastases. The goal of this study was to analyze clinical outcomes and prognostic factors for survival in the salvage setting.

METHODS:
The authors retrospectively examined 79 consecutive breast cancer patients who received salvage SRS (interval of >3 months after initial therapy), 76 of whom (96%) received prior whole-brain radiation therapy. Overall survival (OS) and central nervous system (CNS) progression-free survival rates were calculated from the date of SRS using the Kaplan-Meier method. Prognostic factors were evaluated using the Cox proportional hazards model.

RESULTS:
Median age was 50.5 years. Fifty-eight percent of this population was estrogen receptor positive, 62% was HER2 positive, and 10% was triple negative. At the time of SRS, 95% had extracranial metastases, with 81% of extracranial metastases at other visceral sites (lung/pleura/liver). Forty-eight percent had stable extracranial disease. Median interval from initial brain metastases therapy to SRS was 8.4 months. Median CNS progression-free survival after SRS was 5.7 months (interquartile range [IQR], 3.6-11 months), and median OS was 9.8 months (IQR, 3.8-18 months). Eighty-two percent of evaluable patients received further systemic therapy after SRS. HER2 status (adjusted hazard ratio [HR], 2.4; P = .008) and extracranial disease status (adjusted HR, 2.7; P = .004) were significant prognostic factors for survival on multivariate analysis.

CONCLUSIONS:
In patients with good Karnofsky performance status, salvage SRS for breast cancer brain metastases is a reasonable treatment option, given an associated median survival in excess of 9 months. Furthermore, patients with HER2-positive tumors at diagnosis or stable extracranial disease at the time of SRS have an improved clinical course, with median survival of >1 year. Cancer 2012. © 2011 American Cancer Society.

Effect of tumor subtype on survival and the graded prognostic assessment for patients with breast cancer and brain metastases.
University of Minnesota Gamma Knife, Minneapolis Radiation Oncology, Minneapolis, MN, USA.
p sperduto@mropa.com

**PURPOSE:**
The diagnosis-specific Graded Prognostic Assessment (GPA) was published to clarify prognosis for patients with brain metastases. This study refines the existing Breast-GPA by analyzing a larger cohort and tumor subtype.

**METHODS AND MATERIALS:**
A multi-institutional retrospective database of 400 breast cancer patients treated for newly diagnosed brain metastases was generated. Prognostic factors significant for survival were analyzed by multivariate Cox regression and recursive partitioning analysis (RPA). Factors were weighted by the magnitude of their regression coefficients to define the GPA index.

**RESULTS:**
Significant prognostic factors by multivariate Cox regression and RPA were Karnofsky performance status (KPS), HER2, ER/PR status, and the interaction between ER/PR and HER2. RPA showed age was significant for patients with KPS 60 to 80. The median survival time (MST) overall was 13.8 months, and for GPA scores of 0 to 1.0, 1.5 to 2.0, 2.5 to 3.0, and 3.5 to 4.0 were 3.4 (n = 23), 7.7 (n = 104), 15.1 (n = 140), and 25.3 (n = 133) months, respectively (p < 0.0001). Among HER2-negative patients, being ER/PR positive improved MST from 6.4 to 9.7 months, whereas in HER2-positive patients, being ER/PR positive improved MST from 17.9 to 20.7 months. The log-rank statistic (predictive power) was 110 for the Breast-GPA vs. 55 for tumor subtype.

**CONCLUSIONS:**
The Breast-GPA documents wide variation in prognosis and shows clear separation between subgroups of patients with breast cancer and brain metastases. This tool will aid clinical decision making and
stratification in clinical trials. These data confirm the effect of tumor subtype on survival and show the Breast-GPA offers significantly more predictive power than the tumor subtype alone.

**J Neurosurg. 2010 Dec;113 Suppl:65-72.**

Gamma Knife surgery for metastatic brain tumors from primary breast cancer: treatment indication based on number of tumors and breast cancer phenotype.

Matsunaga S, Shuto T, Kawahara N, Suenaga J, Inomori S, Fujino H.

Department of Neurosurgery, Yokohama Rosai Hospital, Yokohama, Kanagawa, Japan. shigem@mui.biglobe.ne.jp

**OBJECT:**
The goal of this study was to analyze prognostic factors for local tumor control and survival and indications for initial treatment with the Gamma Knife in patients with up to 10 metastatic brain tumors from primary breast cancer.

**METHODS:**
Outcomes were retrospectively reviewed in 101 women with a total of 600 tumors, who underwent Gamma Knife surgery (GKS) for metastatic brain tumors between April 1992 and December 2008 at 1 institution. The inclusion criteria were up to 10 brain metastases, maximum diameter of tumor < 3 cm, and total tumor volume < 15 cm(3). The exclusion criteria were poor systemic condition, presence of carcinomatous meningitis, and previous whole brain radiation treatment and/or craniotomy.

**RESULTS:**
The mean tumor volume at GKS was 3.7 cm(3) (range 0.016-14.3 cm(3)). The mean margin dose was 19 Gy (range 8-30 Gy). Neuroimaging showed that the local tumor growth control rate was 97%, and the tumor response rate was 82.3%. Larger tumor volume (p = 0.001) and lower margin dose (p = 0.001) were significant adverse prognostic factors for local tumor growth control according to a multivariate analysis. The number of brain metastatic lesions was 4 or fewer in 76 patients and 5 or more in 25 patients. The median overall survival time was 13 months. Multivariate analysis revealed that the presence of extracranial metastases (p = 0.041) and lesions that were not the human epidermal growth factor receptor-2 (HER2)-positive type (p = 0.001) were significant adverse prognostic factors for overall survival. The number of brain metastases was not statistically significant, except for a single metastasis. The median new lesion-free survival time after initial GKS was 9 months. Five or more lesions at initial GKS (p = 0.007) and younger patient age (p = 0.008) reduced survival significantly. The prevention of neurological death after GKS was 93.9% at 1 year, and a lower Karnofsky Performance Scale score (p = 0.009) was the only unfavorable factor. Median overall survival associated with the HER2-positive phenotype was significantly longer than survival associated with the other phenotypes (luminal and triple-negative). There were no statistically significant differences between the 3 breast cancer phenotypes for the incidence of new brain metastases after initial GKS.
CONCLUSIONS:
Initial GKS resulted in excellent local tumor control rates, which were associated with prolonged survival and a low risk of neurological death for patients with up to 10 metastatic brain tumors from primary breast cancer. The authors recommend periodic clinical and neuroradiological follow-up examinations after GKS in patients with 5 or more lesions at initial GKS, because they carry a high risk of development of new brain metastases, and in patients with the HER2-positive phenotype, because they tend to have a favorable prognosis in overall survival. Last, the authors recommend additional GKS or whole-brain radiation treatment for salvage treatment if new brain metastases occur.

Gamma Knife surgery as sole treatment for multiple brain metastases: 2-center retrospective review of 1508 cases meeting the inclusion criteria of the JLGK0901 multi-institutional prospective study.
Tokyo Gamma Unit Center, Tsukiji Neurological Clinic, Tokyo, Japan. gamma-knife.serizawa@nifty.com

OBJECT:
The authors retrospectively reviewed the results of Gamma Knife surgery (GKS) used as the sole treatment for brain metastases in patients who met the eligibility criteria for the ongoing JLGK0901 multi-institutional prospective trial. They also discuss the anticipated results of the JLGK0901 study.

METHODS:
Data from 1508 consecutive cases were analyzed. All of the patients were treated at the Gamma Knife House of Chiba Cardiovascular Center or the Mito Gamma House of Katsuta Hospital between 1998 and 2007 and met the following JLGK0901 inclusion criteria: 1) newly diagnosed brain metastases, 2) 1-10 brain lesions, 3) less than 10 cm(3) volume of the largest tumor, 4) no more than 15 cm(3) total tumor volume, 5) no findings of CSF dissemination, and 6) no impairment of activities of daily living (Karnofsky Performance Scale score < 70) due to extracranial disease. At the initial treatment, all visible lesions were irradiated with GKS without upfront whole-brain radiation therapy. Thereafter, gadolinium-enhanced MR imaging was performed every 2-3 months, and new distant lesions were appropriately retreated with GKS. Patients were divided into groups according to numbers of tumors: Group A, single lesions (565 cases); Group B, 2-4 tumors (577 cases); and Group C, 5-10 tumors (366 cases). The differences in overall survival (OS) were compared between groups.

RESULTS:
The median age of the patients was 66 years (range 19-96 years). There were 963 men and 545 women. The primary tumors were in the lung in 1114 patients, gastrointestinal tract in 179, breast in
105, urinary tract in 66, and other sites in 44. The overall mean survival time was 0.78 years (0.99 years for Group A, 0.68 years for Group B, and 0.62 years for Group C). The differences between Groups A and B (p < 0.0001) and between Groups B and C (p = 0.0312) were statistically significant. Multivariate analysis revealed significant prognostic factors for OS to be sex (poor prognostic factor: male, p < 0.0001), recursive partitioning analysis class (Class I vs Class II and Class II vs III, both p < 0.0001), primary site (lung vs breast, p = 0.0047), and number of tumors (Group A vs Group B, p < 0.0001). However, no statistically difference was detected between Groups B and C (p = 0.1027, hazard ratio 1.124, 95% CI 0.999-1.265).

CONCLUSIONS:
The results of this retrospective analysis revealed an upper CI of 1.265 for the hazard ratio, which was lower than the 1.3 initially set by the JLGK0901 study. The JLGK0901 study is anticipated to show noninferiority of GKS as sole treatment for patients with 5-10 brain metastases compared with those with 2-4 in terms of OS.

Stereotactic radiosurgery as primary and salvage treatment for brain metastases from breast cancer. Clinical article.
Kondziolka D, Kano H, Harrison GL, Yang HC, Liew DN, Niranjan A, Brufsky AM, Flickinger JC, Lunsford LD.
Department of Neurological Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania15213, USA. kondziolka@umc.edu

OBJECT:
To evaluate the role of stereotactic radiosurgery (SRS) in the management of brain metastases from breast cancer, the authors assessed clinical outcomes and prognostic factors for survival.

METHODS:
The records from 350 consecutive female patients who underwent SRS for 1535 brain metastases from breast cancer were reviewed. The median patient age was 54 years (range 19-84 years), and the median number of tumors per patient was 2 (range 1-18 lesions). One hundred seventeen patients (33%) had a single metastasis to the brain, and 233 patients (67%) had multiple brain metastases. The median tumor volume was 0.7 cm(3) (range 0.01-48.9 cm(3)), and the median total tumor volume for each patient was 4.9 cm(3) (range 0.09-74.1 cm(3)).

RESULTS:
Overall survival after SRS was 69%, 49%, and 26% at 6, 12, and 24 months, respectively, with a median survival of 11.2 months. Factors associated with a longer survival included controlled extracranial disease, a lower recursive partitioning analysis (RPA) class, a higher Karnofsky Performance
Scale score, a smaller number of brain metastases, a smaller total tumor volume per patient, the presence of deep cerebral or brainstem metastases, and HER2/neu overexpression. **Sustained local tumor control was achieved in 90% of the patients.** Factors associated with longer progression-free survival included a better RPA class, fewer brain metastases, a smaller total tumor volume per patient, and a higher tumor margin dose. Symptomatic adverse radiation effects occurred in 6% of patients. Overall, the condition of 82% of patients improved or remained neurologically stable.

**CONCLUSIONS:**
Stereotactic radiosurgery was safe and effective in patients with brain metastases from breast cancer and should be considered for initial treatment.

Gamma Knife radiosurgery for brain metastases from primary breast cancer.
Kased N, Binder DK, McDermott MW, Nakamura JL, Huang K, Berger MS, Wara WM, Sneed PK.

Department of Radiation Oncology, University of California, San Francisco, School of Medicine, San Francisco, CA 94143-0226, USA. Norbert.Kased@ucsf.edu

**PURPOSE:**
The relative roles of stereotactic radiosurgery (SRS) vs. whole brain radiotherapy (WBRT) in the treatment of patients with brain metastases from breast cancer remain undefined. In this study, we reviewed our experience with these patients.

**MATERIALS AND METHODS:**
We retrospectively reviewed all patients treated between 1991 and 2005 with Gamma Knife SRS for brain metastases from breast cancer. The actuarial survival and freedom from progression endpoints were calculated using the Kaplan-Meier method.

**RESULTS:**
Between 1991 and 2005, **176 patients underwent SRS for brain metastases from breast cancer.** The median survival time was **16.0 months for 95 newly diagnosed patients** and 11.7 months for 81 patients with recurrent brain metastases. In the newly diagnosed patients, omission of **upfront WBRT did not significantly affect the MST** ($p = .20$), brain freedom from progression ($p = .75$), or freedom from new brain metastases ($p = .83$). Longer survival was associated with age <50 years, Karnofsky performance score $\geq 70$, primary tumor control, estrogen receptor positivity, and Her2/neu overexpression. No association was found between the number of treated brain metastases and the survival time.

**CONCLUSION:**
We have described prognostic factors for breast cancer patients treated with SRS for newly diagnosed or recurrent brain metastases. Most patient subsets had a median survival time of \( \geq 11 \) months. Unexpectedly, upfront WBRT did not appear to improve brain freedom from progression, and a larger number of brain metastases was not associated with a shorter survival time. Breast cancer might be distinct from other primary sites in terms of prognostic factors and the roles of WBRT and SRS for brain metastases.


Predictors of distant brain recurrence for patients with newly diagnosed brain metastases treated with stereotactic radiosurgery alone.

Sawrie SM, Guthrie BL, Spencer SA, Nordal RA, Meredith RF, Markert JM, Cloud GA, Fiveash JB.

Department of Radiation Oncology, University of Alabama School of Medicine, Birmingham, AL, USA. ssawrie@uabmc.edu

**PURPOSE:**

To ascertain predictors of distant brain failure (DBF) in patients treated initially with stereotactic radiosurgery alone for newly diagnosed brain metastases. We hypothesize that these factors may be used to group patients according to risk of DBF.

**METHODS AND MATERIALS:**

We retrospectively analyzed 100 patients with newly diagnosed brain metastases treated from 2003 to 2005 at our Gamma Knife radiosurgery facility. The primary endpoint was DBF. Potential predictors included number of metastases, tumor volume, histologic characteristics, extracranial disease, and use of temozolomide.

**RESULTS:**

One-year actuarial risk of DBF was 61% for all patients. Significant predictors of DBF included more than three metastases (hazard ratio, 3.30; \( p = 0.004 \)), stable or poorly controlled extracranial disease (hazard ratio, 2.16; \( p = 0.04 \)), and melanoma histologic characteristics (hazard ratio, 2.14; \( p = 0.02 \)). These were confirmed in multivariate analysis. Those with three or fewer metastases, no extracranial disease, and nonmelanoma histologic characteristics (\( N = 18 \)) had a median time to DBF of 89 weeks vs. 33 weeks for all others. One-year actuarial freedom from DBF for this group was 83% vs. 26% for all others.

**CONCLUSIONS:**

Independent significant predictors of DBF in our series included number of metastases (more than three), present or uncontrolled extracranial disease, and melanoma histologic characteristics. These factors were combined to identify a lower risk subgroup with significantly longer time to DBF. These patients may be candidates for initial localized treatment, reserving whole-brain radiation therapy for
salvage. Patients in the higher risk group may be candidates for initial whole-brain radiation therapy or should be considered for clinical trials.


Stereotactic radiosurgery for four or more intracranial metastases.

Bhatnagar AK, Flickinger JC, Kondziolka D, Lunsford LD.

Department of Radiation Oncology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, USA.

**PURPOSE:**
To evaluate the outcomes after a single stereotactic radiosurgery procedure for the care of patients with 4 or more intracranial metastases.

**METHODS AND MATERIALS:**
Two hundred five patients with primary malignancies, including non-small-cell lung carcinoma (42%), breast carcinoma (23%), melanoma (17%), renal cell carcinoma (6%), colon cancer (3%), and others (10%) underwent gamma knife **radiosurgery for 4 or more intracranial metastases at one time**. The median number of brain metastases was 5 (range, 4-18) with a median total treatment volume of 6.8 cc (range, 0.6-51.0 cc). Radiosurgery was used as sole management (17% of patients), or in combination with whole brain radiotherapy (46%) or after failure of whole brain radiotherapy (38%). The median marginal radiosurgery dose was 16 Gy (range, 12-20 Gy). The mean follow-up was 8 months.

**RESULTS:**
The median overall survival after radiosurgery for all patients was 8 months. The 1-year local control rate was 71%, and the median time to progressive/new brain metastases was 9 months. Using the Radiation Therapy Oncology Group recursive partitioning analysis (RPA) classification system, the **median overall survivals for RPA classes I, II, and III were 18, 9, and 3 months, respectively** (p < 0.00001). Multivariate analysis revealed total treatment volume, age, RPA classification, and marginal dose as significant prognostic factors. The number of metastases was not statistically significant (p = 0.333).

**CONCLUSION:**
Radiosurgery seems to provide survival benefit for patients with 4 or more intracranial metastases. Because total treatment volume was the most significant predictor of survival, the total volume of brain metastases, rather than the number of metastases, should be considered in identifying appropriate radiosurgery candidates.
Stereotactic radiosurgical treatment of cerebral metastases arising from breast cancer.


Department of Radiation Oncology, University of Texas M. D. Anderson Cancer Center, Houston, TX, USA.

OBJECTIVE:
This study was undertaken to evaluate the outcome of patients undergoing stereotactic radiosurgery (SRS) as primary or salvage treatment of brain metastases arising from breast cancer.

MATERIALS AND METHODS:
Between July 2000 and September 2005, the medical records of 49 breast cancer patients who underwent SRS for 84 brain metastases were reviewed retrospectively. Thirty-four patients received SRS as primary brain metastasis treatment and 15 patients received SRS as salvage treatment of brain metastasis recurrence following prior whole-brain radiation therapy. The Kaplan-Meier method, univariate comparisons with log-rank test, and multivariate analysis were performed.

RESULTS:
Median follow-up was 12 months (range, 5-50 months) and median survival was 19 months for all patients. The 1- and 2-year overall survival (OS) rates were 60%, 56%, and 55%, 23% for initial SRS alone and SRS salvage groups, respectively (P = 0.99). A multivariate analysis showed that a high KPS score (KPS > or =90 vs. <90; P = 0.02), a higher SIR value (SIR > or =6 vs. <6; P = 0.001), postmenopausal status (P = 0.003), and positive estrogen receptor status (P = 0.04) were predictive of better survival. The 1- and 2-year local control rates were 79%, 49%, and 77%, 46% for SRS alone and SRS salvage group, respectively.

CONCLUSION:
SRS can be used as primary treatment of brain metastases or salvage of recurrences after whole-brain radiation therapy to achieve good local control on the order of close to 80% at 1 year. The median survival of brain metastasis patients with breast cancer of 19 months appears favorable compared with the general brain metastasis population.
Gamma knife surgery for the treatment of intracranial metastases from breast cancer.
Goyal S, Prasad D, Harrell F Jr, Matsumoto J, Rich T, Steiner L.

Department of Radiation Oncology, Howard University Hospital, Washington, DC, USA.

OBJECT:
The goal of this study was to evaluate the effectiveness and limitations of gamma knife surgery (GKS) in the treatment of intracranial breast carcinoma lesions.

METHODS:
A retrospective analysis of the GKS database at the University of Virginia Health System identified 43 patients with a total of 84 lesions who were treated between 1989 and 2000. All patients who received treatment were included in this study. Imaging studies were available in 35 patients with 67 treated lesions. The overall duration of median survival was 13 months (95% confidence interval [CI] 7-16 months) after radiosurgery. A univariable Cox regression analysis revealed that a single lesion (p = 0.035), a high Karnofsky Performance Scale (KPS) score (p = 0.019), and a high Score Index for Radiosurgery (SIR) in Brain Metastases (p = 0.036) were associated with a significantly lengthened time to local treatment failure. The median duration of survival for patients grouped according to the SIR as low, middle, and high was 3, 8, and 21 months, respectively (p = 0.00033). A multivariable analysis showed that a high KPS score (p = 0.006), a high SIR (p = 0.014), and advanced age (0.038) were predictive of survival. The 1-, 2-, 3-, and 5-year survival rates were 49, 23, 12, and 2%, respectively. The overall median time to local treatment failure was 10 months (95% CI 6-14 months) after GKS. A univariable analysis demonstrated that a single lesion, higher KPS score, and a higher SIR were associated with a significantly longer time until local treatment failure. A multivariable analysis showed that a higher KPS score and SIR and patients who had received chemotherapy were associated with a significantly longer time to local treatment failure. Neuroimaging scores given for the enhancement pattern (ring-enhancing, heterogeneous, and homogeneous signal), amount of necrosis (none, < 50%, and > 50%), and mass effect (none, mild, moderate, and severe) of each treated lesion did not correlate with survival or local treatment failure.

CONCLUSIONS:
The SIR and the KPS score are prognostic factors in patients whose intracranial breast cancer metastases are treated with GKS. The SIR, which includes the KPS score, patient age, systemic disease status, largest lesion volume, and number of lesions, can be used to identify those patients with breast cancer metastasis who would benefit from GKS better than KPS score alone. The contribution of whole-brain radiation therapy to GKS with regard to local tumor control or survival could not be identified.
**Stereotactic radiosurgery for multiple brain metastases from breast carcinoma.**

Muacevic A, Kreth FW, Tonn JC, Wowra B.
Cancer. 2004 Apr 15;100(8):1705-11

Department of Neurosurgery, Ludwig-Maximilians-University, Klinikum Grosshadern, Munich, Germany. amuacevi@helios.med.uni-muenchen.de

**BACKGROUND:**
The current study analyzed the feasibility and outcome of stereotactic radiosurgery (SRS) for treatment of brain metastases from breast carcinoma.

**METHODS:**
During an 8-year period, 151 patients with a combined total of 620 brain metastases from breast carcinoma underwent 197 outpatient SRS procedures. Sixty-three percent of all patients had multiple brain metastases. The median tumor volume was 2.2 cm$^3$ (range, 0.1-20.9 cm$^3$). The mean prescribed tumor dose was 19 +/- 4 grays. Local/distant tumor recurrences were treated with additional radiosurgical therapy for patients with stable systemic disease. All patients were categorized according to the Radiation Therapy Oncology Group classification. Survival time and freedom from local tumor recurrence were analyzed using the Kaplan-Meier method. Prognostic factors were identified using the Cox proportional hazards model.

**RESULTS:**
The overall median survival duration was 10 months after SRS. Ninety-four percent of patients did not experience local brain tumor recurrence after radiosurgery. In addition, 70.2% of patients did not have disease recurrence in the brain. Most patients died of systemically progressing malignancy. A Karnofsky performance score > 70 and recursive partitioning analysis Class I were related to prolonged survival in the univariate and multivariate analyses. Age, whole-brain radiotherapy, surgery, number of metastases, chemotherapy, and latency period from diagnosis of the primary tumor to the development of brain metastases did not reach prognostic relevance in the multivariate model. Patients with RPA I, II, and III survived 34.9, 9.1, and 7.9 months, respectively. There was no treatment related permanent morbidity and mortality. The transient morbidity rate was 17%. Sixteen patients exhibited symptomatic transient complications related to treatment.

**CONCLUSIONS:**
The results of the current study indicate that SRS is a feasible treatment concept for selected patients with multiple brain metastases from breast carcinoma. Copyright 2004 American Cancer Society.
Gamma knife radiosurgery in the treatment of patients with single and multiple brain metastases from carcinoma of the breast.
Amendola BE, Wolf AL, Coy SR, Amendola M, Bloch L.

Miami Neuroscience Center Coral Gables, Florida, USA.

PURPOSE:
The purpose of the study was to evaluate the results of gamma knife radiosurgery for treatment of brain metastases from carcinoma of the breast.

MATERIALS AND METHODS:
From December 1993 to July 1998, 68 women with breast carcinoma metastatic to the brain were treated with gamma knife radiosurgery at Miami Neuroscience Center in Coral Gables, Florida. The ages ranged from 25 to 80 years, with a median age of 52 years. Thirty-eight patients had previously received conventional modalities of treatment for brain metastases including whole-brain irradiation. A total of 110 treatments were given to the 68 women to an average of eight tumor sites per patient. Minimum doses ranged from 6 to 25 Gy to the 35% to 85% isodose line, with 95% of the prescribed minimum doses ranging from 15 to 24 Gy. Patients were treated for one to three lesions (n = 26), four to seven lesions (n = 18), and eight or more lesions (n = 24).

RESULTS:
The median overall actuarial survival for the entire group was 7.8 months. The actuarial survival was 32% at 1 year. The median follow-up was 7.8 months. Overall local control by lesion was 94% (485/518 lesions), and average tumor volume was 3.3 cm³. Twenty-seven (40%) of 68 eligible patients survived 1 year, nine (13%) survived 2 years, and two (3%) survived more than 3 years. Fifty-one of 56 documented deaths (91%) were unrelated to brain metastases. In a subgroup of 15 patients with single brain metastases, the average tumor volume was 16.6 cm³, and local control was 73% (11/15 lesions). The 15 patients who died had a median survival of 7.7 months (range, 3 to 45.7 months).

CONCLUSIONS:
Gamma knife radiosurgical treatment of patients with brain metastases from carcinoma of the breast has shifted the question of survival to that of systemic control. There was no radiation-induced dementia, and a remarkably low incidence of local failure was seen. Survival has been found to be independent of the number of lesions treated.
**Stereotactic radiosurgery for brain metastases from breast cancer.**
Firlik KS, Kondziolka D, Flickinger JC, Lunsford LD.

Department of Neurological Surgery, University of Pittsburgh Medical Center, Pennsylvania 15213-2582, USA. kfirlik@pop.pitt.edu

**BACKGROUND:**
Stereotactic radiosurgery is an alternative to resection or to radiotherapy alone for patients with brain metastases. Outcomes after radiosurgery for patients with brain metastases specifically from breast cancer have not been defined.

**METHODS:**
We retrospectively studied survival and tumor control for all patients with brain metastases from breast cancer who underwent gamma knife stereotactic radiosurgery at the University of Pittsburgh. Univariate and multivariate analyses were used to determine which prognostic factors significantly affected survival.

**RESULTS:**
Thirty patients underwent **radiosurgery between 1990 and 1997. A total of 58 metastases** were treated. The **median length of survival for all patients was 13 months from radiosurgery** and 18 months from diagnosis of brain metastases. **The tumor control rate on follow-up imaging was 93%.** On multivariate analysis, the only factor that correlated with longer survival was the absence of multiple brain metastases. Age, presence of systemic disease, previous whole brain radiation, location, and total tumor volume did not significantly affect survival. Four patients had tumors with evidence of radiation-induced edema after radiosurgery but did not require resection. Two patients underwent delayed resection for tumor growth after radiosurgery.

**CONCLUSIONS:**
Stereotactic radiosurgery is an effective treatment for brain metastases from breast cancer and is associated with a low complication rate.
2.b. Brain Metastases from Lung Cancer

Patients with a complete response after multimodality therapy for locally advanced non-small cell lung cancer (NSCLC) are at high risk for the subsequent development of brain metastases. Chen found that 55% developed brain metastases (Chen 2007). The 5-year estimates of brain metastasis-free survival for patients with squamous and nonsquamous cancers were 57% and 34%, respectively (Chen 2007).

Local control rates after stereotactic radiosurgery in general were quite consistent between 81% (Sheehan 2005), 94% (Gerosa 2005) and 98% (Serizawa 2002). Tumour control rates after Gamma Knife radiosurgery varied depending of the tumour volume between 94% for metastases between 0.5-2 cm³ and 85.7% for tumours between 8-14 cm³ respectively (Pan 2005). The median survival for patients with brain metastases from lung cancer treated with Gamma Knife ranged between 9 and 18 months. Serizawa demonstrated that Gamma Knife radiosurgery appears to be as effective in treating brain metastases from SCLC as for those from NSCLC (Serizawa 2002). A median overall survival of 18 months was reported in solitary brain metastasis from NSCLC after Gamma Knife treatment plus additional WBRT (in 78%) (Flannery 2008), but generally the combination of WBRT plus Gamma Knife did not provide better survival than Gamma Knife treatment alone (Flannery 2003, Pan 2005, Sheehan 2002).

References (Gamma Knife in the Treatment of Brain Metastases from Lung Cancer)


Selected Literature 2002-2012: Brain Metastases from Lung cancer


Gamma knife stereotactic radiosurgery as salvage therapy after failure of whole-brain radiotherapy in patients with small-cell lung cancer.

Harris S, Chan MD, Lovato JF, Ellis TL, Tatter SB, Bourland JD, Munley MT, Deguzman AF, Shaw EG, Urbanic JJ, McMullen KP.

Department of Radiation Oncology, Wake Forest University, Winston-Salem, North Carolina.

**PURPOSE:**

Radiosurgery has been successfully used in selected cases to avoid repeat whole-brain irradiation (WBI) in patients with multiple brain metastases of most solid tumor histological findings. Few data are available for the use of radiosurgery for small-cell lung cancer (SCLC).

**METHODS AND MATERIALS:**

Between November 1999 and June 2009, **51 patients with SCLC and previous WBI** and new brain metastases were treated with GammaKnife stereotactic radiosurgery (GKSRS). A median dose of 18 Gy (range, 10-24 Gy) was prescribed to the margin of each metastasis. Patients were followed with serial imaging. Patient electronic records were reviewed to determine disease-related factors and clinical outcomes after GKSRS. Local and distant brain failure rates, overall survival, and likelihood of neurologic death were determined based on imaging results. The Kaplan-Meier method was used to determine survival and local and distant brain control. Cox proportional hazard regression was performed to determine strength of association between disease-related factors and survival.

**RESULTS:**

Median survival time for the entire cohort was **5.9 months**. Local control rates at 1 and 2 years were **57% and 34%**, respectively. Distant brain failure rates at 1 and 2 years were **58% and 75%**, respectively. Fifty-three percent of patients ultimately died of neurologic death. On multivariate analysis, patients with stable (hazard ratio [HR] = 2.89) or progressive (HR = 6.98) extracranial disease (ECD) had worse overall survival than patients without evidence of ECD (p = 0.00002). Concurrent chemotherapy improved local control (HR = 89; p = 0.006).
CONCLUSIONS:
GKSRS represents a feasible salvage option in patients with SCLC and brain metastases for whom previous WBI has failed. The status of patients’ ECD is a dominant factor predictive of overall survival. Local control may be inferior to that seen with other cancer histological results, although the use of concurrent chemotherapy may help to improve this.

IMPORTANT (large series)
Gamma knife radiosurgery for treatment of cerebral metastases from non-small-cell lung cancer.
Radiotherapy Department, San Raffaele Scientific Institute, Milan, Italy. mail: motta.micaela@hsr.it

PURPOSE:
To evaluate clinical and physico-dosimetric variables affecting clinical outcome of patients treated with Gamma Knife radiosurgery (GKRS) for brain metastases from non-small cell lung cancer (NSCLC).

METHODS AND MATERIALS:
Between 2001 and 2006, 373 patients (298 men and 75 women, median age 65 years) with brain metastases from NSCLC underwent GKRS. All of them had KPS ≥ 60%, eight or fewer brain metastases, confirmed histopathological diagnosis and recent work-up (<3 months). Thirty-five patients belonged to recursive partitioning analysis (RPA) Class I, 307 patients were in RPA Class II, 7 patients were in RPA Class III. Median tumor volume was 3.6 cm³. Median marginal dose was 22.5 Gy at 50% isodose.; median 10 Gy and 12 Gy isodose volumes were 30.8 cm³ and 15.8 cm³, respectively. Follow-up with MRI was performed every 3 months. Overall survival data were collected from internal database, telephone interviews, and identifying registries.

RESULTS:
Mean follow-up after GKRS was 51 months (range, 6 to 96 months); mean overall survival was 14.2 months. Of 373 patients, 29 were alive at time of writing, 104 had died of cerebral progression, and 176 had died of systemic progression. In 64 cases it was not possible to ascertain the cause. Univariate and multivariate analysis were adjusted for the following: RPA class, surgery, WBRT, age, gender, number of lesions, median tumor volume, median peripheral dose, and 10 Gy and 12 Gy volumes. Identified RPA class and overall tumor volume >5 cc were the only two covariates independently predictive of overall survival in patients who died of cerebral progression.
CONCLUSIONS:
Global volume of brain disease should be the main parameter to consider for performing GKRS, which is a first-line therapy for patient in good general condition and controlled systemic disease.

IMPORTANT: large series
Radiosurgery for non-small cell lung carcinoma metastatic to the brain: long-term outcomes and prognostic factors influencing patient survival time and local tumor control.
Sheehan JP, Sun MH, Kondziolka D, Flickinger J, Lunsford LD.
Department of Neurological Surgery, University of Pittsburgh Medical Center, Presbyterian Hospital, Pittsburgh, Pennsylmania, USA. jps2f@virginia.edu

OBJECT:
Lung carcinoma is the leading cause of death from cancer. More than 25% of those patients with lung cancer develop a brain metastasis at some time during the course of their disease. Corticosteroid therapy, radiotherapy, and resection have been the mainstays of treatment. Nonetheless, the median survival for patients with lung carcinoma metastasis is approximately 3 to 6 months. The authors examine the efficacy of gamma knife radiosurgery (GKS) for treating non-small cell lung carcinoma (NSCLC) metastases to the brain and evaluate factors affecting long-term patient survival.

METHODS:
A retrospective review of 273 patients who had undergone GKS to treat a total of 627 NSCLC metastases was performed. Clinical and neuroimaging data encompassing a 14-year treatment interval were collected. Univariate and multivariate analyses were performed to determine significant prognostic factors influencing patient survival. The overall median patient survival time was 15 months (range 1-116 months) from the diagnosis of brain metastases. The median survival was 10 months from GKS treatment in those patients with adenocarcinoma and 7 months for those with other histological tumor types. In patients with no active extracranial disease at the time of GKS, the median survival time was 16 months. In multivariate analyses, factors significantly affecting survival included: 1) female sex (p = 0.014); 2) preoperative Karnofsky Performance Scale score (p < 0.0001); 3) adenocarcinoma histological subtype (p = 0.0028); 4) active systemic disease (p = 0.0001); and 5) time from lung cancer diagnosis to the development of brain metastasis (p = 0.0074). Prior tumor resection or whole-brain radiation therapy did not correlate with extended patient survival time.
Postradiosurgical imaging of brain metastases revealed that 60% decreased, 24% remained stable, and 16% eventually increased in size. Factors affecting local tumor control included tumor volume (p = 0.042) and treatment isodose (p = 0.015). Fourteen patients (5.1%) later underwent craniotomy and tumor resection for tumor refractory to GKS or a new symptomatic metastasis.
CONCLUSIONS:
Gamma knife surgery for NSCLC metastases affords effective local tumor control in approximately 84% of patients. Early detection of brain metastases, aggressive treatment of systemic disease, and a therapeutic strategy including GKS can afford patients an extended survival time.

IMPORTANT: large series
Gamma knife radiosurgery for metastatic brain tumors from lung cancer: a comparison between small cell and non-small cell carcinoma.
Department of Neurosurgery, Chiba Cardiovascular Center, Ichihara, Japan. QWT03231@nifty.ne.jp

OBJECT:
The purpose of this retrospective study was to evaluate the effectiveness of gamma knife radiosurgery (GKS) for the treatment of metastatic brain tumors from lung cancer, with particular reference to small cell lung carcinoma (SCLC) compared with non-SCLC (NSCLC).

METHODS:
Two hundred forty-five consecutive patients meeting the following five criteria were evaluated in this study: 1) no prior brain tumor treatment; 2) 25 or fewer lesions; 3) a maximum of three tumors with a diameter of 20 mm or larger; 4) no surgically inaccessible tumor 30 mm or greater in diameter; and 5) more than 3 months of life expectancy. According to the same treatment protocol, large tumors (> or = 30 mm) were surgically removed and the other small lesions (< 30 mm) were treated with GKS. New lesions were treated with repeated GKS. Chemotherapy was administered, according to the primary physician's protocol, as aggressively as possible. Progression-free, overall, neurological, qualitative, and new lesion-free survival were calculated with the Kaplan-Meier method and were compared in the SCLC and NSCLC groups by using the log-rank test. The poor prognostic factors for each type of survival were also analyzed with the Cox proportional hazard model.

CONCLUSIONS:
Tumor control rate at 1 year was 94.5% in the SCLC group and 98% in the NSCLC group. The median survival time was 9.1 months in the SCLC group and 8.6 months in the NSCLC group. The 1-year survival rates in the SCLC group were 86.5% for neurological survival and 68.9% for qualitative survival; those in the NSCLC group were 87.9% for neurological and 78.9% for qualitative survival. The estimated median interval to emergence of a new lesion was 6.9 months in the SCLC group and 9.8 months in the NSCLC group. There was no significant difference between the two groups for any type of survival; this finding was verified by multivariate analysis. The results of this
study suggest that GKS appears to be as effective in treating brain metastases from SCLC as for those from NSCLC.

IMPORTANT: COMPARISON GK vs. WBRT

Gamma knife radiosurgery for multiple brain metastases from lung cancer.
Park SH, Hwang SK, Kang DH, Lee SH, Park J, Hwang JH, Hamm IS, Park YM.
Department of Neurosurgery, BioMedical Research Institute, Kyungpook National University Hospital 50, Samduk-2-ga, Jung-gu, Daegu 700-721, South Korea. nsdoctor@naver.com

The aim of this study was to compare the effectiveness of gamma knife radiosurgery (GKS) for the treatment of multiple brain metastases from lung cancer with that of whole brain radiation therapy (WBRT). Patients with multiple (2-20) brain metastases were divided into two groups for initial brain tumor management: a **GKS group (14 patients)** and a **WBRT group (19 patients)**. The patients were stratified by gender, age, initial Karnofsky performance status score, control of the primary site, known extracranial metastases, number of brain metastases, diameter of the maximal lesion, chemotherapy, and recursive partitioning analysis (RPA) Class. The **6-month and 1-year overall survival rates were 64.3% and 47.7%, respectively, in the GKS group, and 42.1% and 10.5%, respectively, in the WBRT group.** The median survival time was 32 weeks in the GKS group and 24 weeks in the WBRT group. The **overall survival time in the GKS group was significantly longer than in the WBRT group (p=0.04).** The univariate analysis suggests that survival was increased in both patients with a controlled primary tumor site and in the GKS group (p=0.03, 0.04). The use of GKS in patients with multiple brain metastases significantly improved patient survival compared to the employment of WBRT. When we assessed the subgroups, systemic disease control and GKS were significant variables by univariate analysis.

Stereotactic radiosurgery for patients with brain metastases from small cell lung cancer.
Wegner RE, Olson AC, Kondziolka D, Niranjan A, Lundsford LD, Flickinger JC.
Department of Radiation Oncology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.

BACKGROUND:

Patients with small-cell lung cancer have a high likelihood of developing brain metastases. Many of these patients will have prophylactic cranial irradiation (PCI) or eventually undergo whole brain radiation therapy (WBRT). Despite these treatments, a large number of these patients will have progression of
their intracranial disease and require additional local therapy. Stereotactic radiosurgery (SRS) is an important treatment option for such patients.

METHODS:
We retrospectively reviewed the charts of 44 patients with brain metastases from small-cell lung cancer treated with gamma knife SRS. Multivariate analysis was used to determine significant prognostic factors influencing survival.

RESULTS:
The median follow-up from SRS in this patient population was 9 months (1-49 months). The median overall survival (OS) was 9 months after SRS. Karnofsky performance status (KPS) and combined treatment involving WBRT and SRS within 4 weeks were the two factors identified as being significant predictors of increased OS (p = 0.033 and 0.040, respectively). When comparing all patients, patients treated with a combined approach had a median OS of 14 months compared to 6 months if SRS was delivered alone. We also compared the OS times from the first definitive radiation: WBRT, WBRT and SRS if combined therapy was used, and SRS if the patient never received WBRT. The median survival for those groups was 12, 14, and 13 months, respectively, p = 0.19. Seventy percent of patients had follow-up magnetic resonance imaging available for review. Actuarial local control at 6 months and 12 months was 90% and 86%, respectively. Only 1 patient (2.2%) had symptomatic intracranial swelling related to treatment, which responded to a short course of steroids. New brain metastases outside of the treated area developed in 61% of patients at a median time of 7 months; 81% of these patients had received previous WBRT.

CONCLUSIONS:
Stereotactic radiosurgery for small-cell lung carcinoma brain metastases provided safe and effective local tumor control in the majority of patients.

Gamma knife radiosurgery in non small cell lung cancer patients with brain metastases: treatment results and prognostic factors.
Abacioglu U, Caglar H, Atasoy BM, Abdulloev T, Akgun Z, Kilic T.
Marmara University Hospital, School of Medicine, Department of Radiation Oncology, Istanbul, Turkey.

PURPOSE:
To evaluate the efficacy of gamma knife radiosurgery (GKRS) for the treatment of brain metastases from non small cell lung cancer (NSCLC) and find out the prognostic factors for overall survival.
METHODS:
Between February 1997 and August 2003 100 patients underwent treatment for 184 brain metastases from NSCLC, either for recurrence (n=49) or with a new diagnosis (n=51). Median age was 55 years and 77 patients were male. Seventy-eight of the patients received whole brain radiotherapy (WBRT) prior to or after GKRS and 26 patients had surgical removal of the metastasis. Imaging and clinical status were monitored every 3 months following treatment. Kaplan-Meier survival curves, Cox proportional hazards regression for risk factor analysis were used.

RESULTS:
The median follow up after the procedure was 8 months and after the diagnosis 11 months. The median overall survival for all patients was 9 months from the date of GKRS and 14 months from the diagnosis of brain metastasis. Local tumor control was achieved in 95% of the lesions. In multivariate analysis, adenocarcinoma histology, Karnofsky performance status (KPS) score > 80, 1-3 metastases and tumor diameter <2 cm were related to longer survival. Addition of WBRT did not have any effect on overall survival.

CONCLUSION:
Gamma knife surgery appears to be effective in treating patients with brain metastases from NSCLC, either alone or with WBRT in selected groups of patients.

Gamma Knife radiosurgery to the surgical cavity following resection of brain metastases.
Department of Neurological Surgery, University of Virginia Health Sciences Center, Charlottesville, VA 22908, USA.

OBJECT:
This study evaluated the efficacy of postoperative Gamma Knife surgery (GKS) to the tumor cavity following gross-total resection of a brain metastasis.

METHODS:
A retrospective review was conducted of 700 patients who were treated for brain metastases using GKS. Forty-seven patients with pathologically confirmed metastatic disease underwent GKS to the postoperative resection cavity following gross-total resection of the tumor. Patients who underwent subtotal resection or who had visible tumor in the resection cavity on the postresection neuroimaging study (either CT or MR imaging with and without contrast administration) were excluded. Radiographic and clinical follow-up was assessed using clinic visits and MR imaging. The radiographic end point was defined as tumor growth control (no tumor growth regarding the resection cavity, and
stable or decreasing tumor size for the other metastatic targets). Clinical end points were defined as functional status (assessed prospectively using the Karnofsky Performance Scale) and survival. Primary tumor pathology was consistent with lung cancer in 19 cases (40%), melanoma in 10 cases (21%), renal cell carcinoma in 7 cases (15%), breast cancer in 7 cases (15%), and gastrointestinal malignancies in 4 cases (9%). The mean duration between resection and radiosurgery was 15 days (range 2-115 days). The mean volume of the treated cavity was 10.5 cm³ (range 1.75-35.45 cm³), and the mean dose to the cavity margin was 19 Gy. In addition to the resection cavity, 34 patients (72%) underwent GKS for 116 synchronous metastases observed at the time of the initial radiosurgery.

RESULTS:
The mean radiographic follow-up duration was 14 months (median 10 months, range 4-37 months). Local tumor control at the site of the surgical cavity was achieved in 44 patients (94%), and tumor recurrence at the surgical site was statistically related to the volume of the surgical cavity (p=0.04). During follow-up, 34 patients (72%) underwent additional radiosurgery for 140 new (metachronous) metastases. At the most recent follow-up evaluation, 11 patients (23%) were alive, whereas 36 patients had died (mean duration until death 12 months, median 10 months). Patients who showed good systemic control of their primary tumor tended to have longer survival durations than those who did not (p=0.004). At the last clinical follow-up evaluation, the mean Karnofsky Performance Scale score for the overall group was 78 (median 80, range 40-100).

CONCLUSION:
Radiosurgery appears to be effective in terms of providing local tumor control at the resection cavity following resection of a brain metastasis, and in the treatment of synchronous and metachronous tumors. These data suggest that radiosurgery can be used to prevent recurrence following gross-total resection of a brain metastasis.

Gamma knife radiosurgery for ten or more brain metastases.
Kim CH, Im YS, Nam DH, Park K, Kim JH, Lee JI.
Department of Neurosurgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

OBJECTIVE:
This study was performed to assess the efficacy of GKS in patients with ten or more brain metastases.

METHODS:
From Aug 2002 to Dec 2007, twenty-six patients (13 men and 13 women) with ten or more cerebral metastatic lesions underwent GKS. The mean age was 55 years (32-80). All patients had Karnofsky performance status (KPS) score of 70 or better. According to recursive partitioning analysis (RPA)
classification, 3 patients belonged to class I and 23 to class II. The location of primary tumor was lung (21), breast (3) and unknown (2). The mean number of the lesions per patient was 16.6 (10-37). The mean cumulated volume was 10.9 cc (1.0-42.2). The median marginal dose was 15 Gy (9-23). Overall survival and the prognostic factors for the survival were retrospectively analyzed by using Kaplan Meier method and univariate analysis.

RESULTS:
Overall median survival from GKS was 34 weeks (8-199). Local control was possible for 79.5% of the lesions and control of all the lesions was possible in at least 14 patients (53.8%) until 6 months after GKS. New lesions appeared in 7 (26.9%) patients during the same period. At the last follow-up, 18 patients died; 6 (33.3%) from systemic causes, 10 (55.6%) from neurological causes, and 2 (11.1%) from unknown causes. Synchronous onset in non-small cell lung cancer (p=0.007), high KPS score (>/=80, p=0.029), and controlled primary disease (p=0.020) were favorable prognostic factors in univariate analysis.

CONCLUSION:
In carefully selected patients, GKS may be a treatment option for ten or more brain metastases.

Long-term survival in patients with synchronous, solitary brain metastasis from non-small-cell lung cancer treated with radiosurgery.

Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, MD 21201, USA.

PURPOSE:
To report the outcome of patients with synchronous, solitary brain metastasis from non-small-cell lung cancer (NSCLC) treated with gamma knife stereotactic radiosurgery (GKSRS).

PATIENTS AND METHODS:
Forty-two patients diagnosed with synchronous, solitary brain metastasis from NSCLC were treated with GKSRS between 1993 and 2006. The median Karnofsky performance status (KPS) was 90. Patients had thoracic Stage I-III disease (American Joint Committee on Cancer 2002 guidelines). Definitive thoracic therapy was delivered to 26/42 (62%) patients; 9 patients underwent chemotherapy and radiation, 12 patients had surgical resection, and 5 patients underwent preoperative chemoradiation and surgical resection.
RESULTS:
The median overall survival (OS) was 18 months. The 1-, 2-, and 5-year actuarial OS rates were 71.3%, 34.1%, and 21%, respectively. For patients who underwent definitive thoracic therapy, the median OS was 26.4 months compared with 13.1 months for those who had nondefinitive therapy, and the 5-year actuarial OS was 34.6% vs. 0% (p < 0.0001). Median OS was significantly longer for patients with a KPS ≥90 vs. KPS < 90 (27.8 months vs. 13.1 months, p < 0.0001). The prognostic factors significant on multivariate analysis were definitive thoracic therapy (p = 0.020) and KPS (p = 0.001).

CONCLUSIONS:
This is one of the largest series of patients diagnosed with synchronous, solitary brain metastasis from NSCLC treated with GKSRS. Definitive thoracic therapy and KPS significantly impacted OS. The 5-year OS of 21% demonstrates the potential for long-term survival in patients treated with GKSRS; therefore, patients with good KPS should be considered for definitive thoracic therapy.

Prognosis of non-small cell lung cancer with synchronous brain metastases treated with gamma knife radiosurgery.
Kong DS, Lee JI, Nam DH, Park K, Kim JH, Kim JG, Park JO, Park K.

Department of Neurosurgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

The clinical outcome and prognostic factors of patients with synchronous brain metastases from non-small cell lung cancer (NSCLC) who were treated with gamma knife radiosurgery (GKS) were analyzed. A total of 35 patients with NSCLC underwent GKS as an initial treatment for metastatic brain lesions of synchronous onset. The period of survival and various prognostic factors such as age, gender, performance status, multiplicity of the brain lesions, intracranial tumor volume, and extent of the primary tumor were analyzed. The overall median survival time for this series was 12 months (range 0.75 to 43 months) from the diagnosis. Of the 21 patients who were no longer alive at the conclusion of this study, only 7 (33.3%) died of neurological causes. Multivariate analysis of these data revealed that N stage, whole-brain radiotherapy (WBRT), and chemotherapy were significant predictors for survival (p<0.05). Survival of patients with NSCLC and synchronous brain metastases is mainly dependent upon the progression of the systemic disease, provided that the cerebral lesions are treated adequately with local treatment modalities including radiosurgery. Application of radiosurgery as an initial treatment option and aggressive local and systemic modalities to control extracranial disease may improve survival.
Cancer. 2007 Apr 15;109(8):1668-75
Risk of cerebral metastases and neurological death after pathological complete response to neoadjuvant therapy for locally advanced nonsmall-cell lung cancer: clinical implications for the subsequent management of the brain.
Chen AM, Jahan TM, Jablons DM, Garcia J, Larson DA.

Department of Radiation Oncology, University of California, San Francisco (UCSF), School of Medicine, San Francisco, California, USA. allenmchen@yahoo.com

BACKGROUND:
The incidence and pattern of brain metastases was analyzed among patients who achieved a pathological complete response (pCR) after neoadjuvant chemotherapy or chemoradiotherapy for locally advanced nonsmall-cell lung cancer (NSCLC).

METHODS:
Between 1990 and 2004, 211 patients were treated with neoadjuvant therapy before surgical resection for stage III NSCLC. The clinical course of 51 patients who demonstrated a pCR were reviewed. The neoadjuvant regimen consisted of either chemotherapy (29 patients) or chemoradiotherapy (22 patients). Histology was 45% adenocarcinoma, 41% squamous cell, and 14% large cell carcinoma. No patient received prophylactic cranial irradiation (PCI).

RESULTS:
Overall survival at 1, 3, and 5 years was 82%, 63%, and 42%, respectively. The most common site of initial recurrence was the brain. Twenty-two (43%) patients developed brain metastasis as the site of first failure, which represented 71% of all isolated recurrences. Ultimately, 28 (55%) patients developed brain metastases at some point during their clinical course. The 5-year estimates of brain metastasis-free survival for patients with squamous and nonsquamous cancers were 57% and 34%, respectively (P = .02). Median survival from the time of brain metastasis was 10 and 5 months for those with isolated and nonisolated recurrences, respectively.

CONCLUSION:
Patients with a pCR after multimodality therapy for locally advanced NSCLC are at excessively high risk for the subsequent development of brain metastases. Implications for management strategies including PCI and stereotactic radiosurgery (SRS) are discussed.

Prognosis of non-small cell lung cancer with synchronous brain metastases treated with gamma knife radiosurgery.
Kong DS, Lee JI, Nam DH, Park K, Kim JH, Kim JG, Park JO, Park K.

Department of Neurosurgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

The clinical outcome and prognostic factors of patients with synchronous brain metastases from non-small cell lung cancer (NSCLC) who were treated with gamma knife radiosurgery (GKS) were analyzed. A total of 35 patients with NSCLC underwent GKS as an initial treatment for metastatic brain lesions of synchronous onset. The period of survival and various prognostic factors such as age, gender, performance status, multiplicity of the brain lesions, intracranial tumor volume, and extent of the primary tumor were analyzed. The overall median survival time for this series was 12 months (range 0.75 to 43 months) from the diagnosis. Of the 21 patients who were no longer alive at the conclusion of this study, only 7 (33.3%) died of neurological causes. Multivariate analysis of these data revealed that N stage, whole-brain radiotherapy (WBRT), and chemotherapy were significant predictors for survival (p<0.05). Survival of patients with NSCLC and synchronous brain metastases is mainly dependent upon the progression of the systemic disease, provided that the cerebral lesions are treated adequately with local treatment modalities including radiosurgery. Application of radiosurgery as an initial treatment option and aggressive local and systemic modalities to control extracranial disease may improve survival.


Radiosurgery for patients with recurrent small cell lung carcinoma metastatic to the brain: outcomes and prognostic factors.
Sheehan J, Kondziolka D, Flickinger J, Lunsford LD.

Department of Neurological Surgery, University of Virginia, Charlottesville, Virginia 22908, USA.
jps2f@virginia.edu

OBJECT:
Lung carcinoma is the leading cause of death from cancer. More than 50% of those with small cell lung cancer develop a brain metastasis. Corticosteroid agents, radiotherapy, and resection have been the mainstays of treatment. Nonetheless, median survival for patients with small cell lung carcinoma metastasis is approximately 4 to 5 months after cranial irradiation. In this study the authors examine the efficacy of gamma knife surgery for treating recurrent small cell lung carcinoma.
metastases to the brain following tumor growth in patients who have previously undergone radiation therapy, and they evaluate factors affecting survival.

METHODS:
A retrospective review of 27 patients (47 recurrent small cell lung cancer brain metastases) undergoing radiosurgery was performed. Clinical and radiographic data obtained during a 14-year treatment period were collected. Multivariate analysis was utilized to determine significant prognostic factors influencing survival. The overall median survival was 18 months after the diagnosis of brain metastases. In multivariate analysis, factors significantly affecting survival included: 1) tumor volume (p = 0.0042); 2) preoperative Karnofsky Performance Scale score (p = 0.0035); and 3) time between initial lung cancer diagnosis and development of brain metastasis (p = 0.0127). Postradiosurgical imaging of the brain metastases revealed that 62% decreased, 19% remained stable, and 19% eventually increased in size. One patient later underwent a craniotomy and tumor resection for a tumor refractory to radiosurgery and radiation therapy. In three patients new brain metastases were demonstrating on follow-up imaging.

CONCLUSIONS:
Stereotactic radiosurgery for recurrent small cell lung carcinoma metastases provided effective local tumor control in the majority of patients. Early detection of brain metastases, aggressive treatment of systemic disease, and a therapeutic strategy including radiosurgery can extend survival.

Gamma knife surgery for brain metastases from lung cancer.
Pan HC, Sheehan J, Stroila M, Steiner M, Steiner L.

Lars Leksell Center of Gamma Surgery, Department of Neurological Surgery, University of Virginia, Charlottesville, Virginia 22908, USA.

OBJECT:
The authors conducted a study to evaluate the safety and efficacy of gamma knife surgery (GKS) for the treatment of brain metastases from lung cancer.

METHODS:
Between February 1993 and May 2003 191 patients underwent treatment for 424 brain metastases from non-small (171 cases) and small cell lung carcinoma (20 cases). Imaging and clinical status were monitored every 3 months following the treatment. Kaplan-Meier survival curves, Cox proportional hazards regression for risk factor analysis, and nonparametric methods for evaluating tumor response were used. There was no difference in median survival following combined whole-brain radiation therapy (WBRT) and gamma knife surgery (14 months) and GKS alone (15 months). There was also no difference between the median survival rates for either tumor
type. In the multivariate analysis, age less than 65 years, Karnofsky Performance Scale score greater than 70, normal neurological status, multiple GKS treatments, and pre-GKS craniotomy were related to longer survival. Tumor control rates varied according to the volume of the metastases and were as follows: 84.4% (< 0.5 cm3), 94% (0.5-2 cm3), 89.1% (2-4 cm3), 93.4% (4-8 cm3), 85.7% (8-14 cm3), and 87.5% (> 14 cm3). Four lesions required post-GKS craniotomy due to swelling or rapid tumor progression. The rate of tumor shrinkage was higher when a volume was 2 cm3, lower in cystic lesions, lower in tumors with previous WBRT, and lower for margin doses less than 14 Gy.

CONCLUSIONS:
The risk-benefit ratio of GKS in this series was satisfactory. **There was no difference in response rates of the two tumor types, and WBRT did not improve the duration of survival.**

Analysis of long-term outcomes and prognostic factors in patients with non-small cell lung cancer brain metastases treated by gamma knife radiosurgery.
Gerosa M, Nicolato A, Foroni R, Tomazzoli L, Bricolo A.
Department of Neurological and Vision Sciences, University Hospital, Verona, Italy.
massimo.gerosa@univr.it

OBJECT:
The authors conducted a study to evaluate the long-term outcomes and prognostic factors for survival in a large series of patients treated by gamma knife surgery (GKS) for non-small cell lung cancer (NSCLC) brain metastases.

METHODS:
The study is based on the retrospective analysis of clinical and radiological records obtained during a **10-year period (1993-2003), concerning 836 lesions in 504 patients.** The lesions were primary in 86% and recurrent 14% of the cases; they were solitary in 31%, single in 29%, and multiple in 40%. The mean follow-up period was 16 months (range 4-113 months). The most common histological types were adenocarcinoma (51%) and squamous cell carcinoma (27%). Dose planning parameters were as follows: mean target volume 6.2 cm3 (range 0.06-22.5 cm3); mean prescription dose 21.4 Gy (range 15.5-28 Gy); and mean number of isocenters 6.7 (range one-18). Progression-free and actuarial survival curves were calculated using the Kaplan-Meier method. The main factors affecting survival were determined by unimultivariate analysis (log-rank test and Cox proportional hazard models). Analysis of long-term outcomes seemed to confirm that GKS is a primary therapeutic option in these patients. **The 1-year local tumor control rate was 94%. The overall median survival was 14.5 months,** with extremely rewarding quality of life indices. The recursive partitioning analysis classification was the dominant prognostic factor.
CONCLUSIONS:
Gamma knife surgery is a useful treatment for brain metastases from NSCLC.

J Neurosurg. 2004 May;100(5):842-7
Gamma knife surgery in the management of brain metastases from lung carcinoma: a retrospective analysis of survival, local tumor control, and freedom from new brain metastasis.
Department of Neurosurgery, Louisiana State University Health Sciences Center, Shreveport, Louisiana 71130-3932, USA.

OBJECT:
The objective of this retrospective study was to analyze the results of stereotactic radiosurgery performed using a gamma knife in the treatment of 44 consecutive patients with brain metastases from lung carcinoma.

METHODS:
Forty-four patients with lung carcinoma were treated for metastatic brain tumors by performing radiosurgery with a Leksell Gamma Knife. Twenty-one patients (47.7%) were women and 23 were men. The mean age of the patients was 56 years (range 35-77 years). Twenty-two patients (50%) had solitary tumors and the rest had multiple tumors (two-six lesions). Eighteen patients (40.9%) presented with a recurrent and/or progressive brain disease that previously had been treated with other modalities (surgery, external-beam radiotherapy, or both). Fifteen patients had controlled lung disease and 19 patients had systemic metastases (in lymph nodes, liver, and/or bones) at the time of radiosurgery. The median follow-up period was 18.25 months. All patients were followed up for three different end points: 1) death caused by the disease; 2) clinical and/or radiological evidence of progression of the tumor that had been treated with radiosurgery; and 3) appearance of new lesions. At the last follow-up review, 17 patients (38.6%) were alive and 27 (61.4%) had died. Ten patients (22.7%) died as a result of brain disease (failure of local control or new metastases). Controlled primary disease at the time of detection of metastases and the ability to achieve local tumor control after radiosurgery significantly improved the patient survival (p < 0.01). Control of the treated tumor(s) was achieved in 32 of 44 patients (72 tumors) and 10 patients experienced treatment failure. In addition to the 44 patients comprising the study population, two other patients were treated, but died of lung disease too early in the follow-up period to have been assessed. As of the last follow-up review, no new brain metastasis had occurred in 36 patients (81.8% [includes surviving and nonsurviving patients]).
The median duration of overall survival was 7 months, the median period of controlled brain disease was 21 months, and the median period of freedom from new brain metastases was 17 months (95% confidence interval 13-19 months).

CONCLUSIONS:
Gamma knife surgery has significantly reduced the incidence of mortality from brain disease by effectively accomplishing local tumor control in patients with metastatic lung cancer. Local control and freedom from new brain metastases is not influenced by prior external-beam radiotherapy.

Lung Cancer. 2003 Dec;42(3):327-33.

Gamma knife stereotactic radiosurgery for synchronous versus metachronous solitary brain metastases from non-small cell lung cancer.

Department of Radiation Oncology, University of Maryland School of Medicine, 22 South Greene Street, Baltimore, MD 21201, USA.

A retrospective study was conducted analyzing the clinical outcome and various prognostic factors in patients treated with gamma knife stereotactic radiosurgery (GK-SRS) for solitary brain metastasis from non-small cell lung carcinoma (NSCLC). A total of 72 patients from June of 1992 to January of 1999 were treated. All patients received GK-SRS to a median dose of 18Gy, with 45 patients receiving additional whole-brain radiation therapy. No one had evidence of extra-cranial metastasis at the time of diagnosis of brain metastases. The median follow-up was 15.7 months for the entire population and 99.5 months for those who were alive at the last follow-up. Univariate and multivariate analyses were used to test the impact of various prognostic factors on survival. The median and 5-year actuarial survivals for the entire cohort were 15.7 months and 10.4%, respectively. The presence of a metachronous versus a synchronous brain metastasis was the only factor significant in the univariate (P=0.045) and multivariate (P=0.002) analyses. Patients with metachronous solitary brain metastases had a significant median survival advantage compared to those with synchronous metastases (33.3 months versus 8.6 months, P=0.001). However, there was no statistically significant difference in median survival from the time of metastasis when treated with GK-SRS in these groups (12.5 months versus 8.4 months, P=0.50). The addition of WBRT did not improve overall survival (12.0 months versus 7.7 months, P=0.73). The 5-year actuarial survival for the metachronous and synchronous groups were 13.2 and 8.1%, respectively. In conclusion, patients presenting with a solitary metachronous brain metastasis from NSCLC achieved longer survivals than those with a synchronous metastasis. The tail in the survival curves demonstrates that a prolonged survival may be attained in patients with solitary metastases from NSCLC. This study adds to the growing body of literature that supports the use of SRS in the management of this patient population.
2.c. Brain Metastases from Renal Cancer

Brain metastases of renal cell carcinoma are considered radioresistant. After whole brain radiation therapy a survival of only 3.0 months was reported in multiple and 4.4 months for single brain metastases (Wróński 1997). These rather negative results demonstrate the need for a more effective local therapy. A reproducible local control rate between 83 and 96% is generally shown after Gamma Knife treatment of renal cancer metastases with a median survival between 9.5 and 13 months. For RPA classes I median survival was between 18 and 24 months (Muacevic 2004, Hernandez 2002). The addition of WBRT did not prevent the development of new remote tumors in patients with renal cell cancer metastases (Goyal 2000, Mori 1998).

References (Gamma Knife in the Treatment of Metastases from Renal Cancer)


Selected Literature 1997-2011: Brain Metastases from Renal Cancer


Outcome predictors of gamma knife radiosurgery for renal cell carcinoma metastases.

Kano H, Iyer A, Kondziolka D, Niranjan A, Flickinger JC, Lunsford LD.

Department of Neurological Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213, USA.

BACKGROUND:

Although whole-brain radiation therapy (WBRT) has been a standard palliative management for brain metastases from renal cell carcinoma, its benefit has been elusive because of radiobiological resistance.
OBJECTIVE:
To evaluate the role of stereotactic radiosurgery (SRS) in the management of brain metastases from renal cell carcinoma.

METHODS:
We reviewed records from 158 consecutive patients (men = 111, women = 47) who underwent SRS for 531 brain metastases from renal cell carcinoma. The median patient age was 61 years (range, 38-83 years), and the median number of tumors per patient was 1 (range, 1-10). Seventy-nine patients (50%) had solitary brain metastasis. Fifty-seven patients (36%) underwent prior WBRT. The median total tumor volume for each patient was 3.0 cm³ (range, 0.09-47 cm).

RESULTS:
The overall survival after SRS was 60%, 38%, and 19% at 6, 12, and 24 months, respectively, with a median survival of 8.2 months. Factors associated with longer survival included younger age, longer interval between primary diagnosis and brain metastases, lower recursive partitioning analysis class, higher Karnofsky performance status, smaller number of brain metastases, and no prior WBRT. Median survival for patients with <2 brain metastases, higher Karnofsky performance status (> 90), and no prior WBRT was 12 months after SRS. Sustained local tumor control was achieved in 92% of patients. Symptomatic adverse radiation effects occurred in 7%. Overall, 70% of patients improved or remained neurologically stable.

LINEAR ACCELERATOR ACCIDENT!


[Dosimetric stereotactic radiosurgical accident: Study of 33 patients treated for brain metastases].
[Article in French]
Centre régional de radiochirurgie stéréotaxique, centre hospitalier universitaire de Toulouse, hôpital Rangueil, 1, avenue Jean-Poulhès, TSA 50032, 31059 Toulouse cedex 9, France. pierre-yves.borius@hotmail.fr

The consequences of a dosimetric radiosurgery accident are not the same as a conventional radiotherapy accident. The objective of this study was to estimate the clinical and radiological outcome of patients treated by radiosurgery for metastasis during the period of the overexposure accident that occurred in the Toulouse Radiosurgery Unit. Between April 2006 and March 2007, 33 patients with 57 metastases were treated in the Toulouse Radiosurgery Unit (Novalis®, BrainLab). An initial error in the estimation of the scatter factors led to an overexposure to radiation. The median age was 55 years [range, 35-85]. Twenty-one patients (64%) harbored a single metastasis. The primary
tumor location was lung (16 cases), kidney (nine cases), breast (four cases), and others (four cases). The mean tumoral volume was 3.2 cm$^3$ [0.04-14.07]. The mean prescribed dose at the isocenter was 20 Gy [range, 10-23], the mean delivered dose was 31.5 Gy [range, 13-52], and the mean overdose was 61.2% [range, 5.6-226.8]. In order to evaluate the consequences of the overdose, three parameters were analyzed: a risk index using dose and volume, the volume of parenchyma that received more than 12 Gy, and the mean dose in a sphere of 20 cm$^3$ surrounding the target volume. Median actuarial survival was 14.1 months, the survival rate was 79.4% at six months, 59.1% at 12 months, and 27.2% at 24 months. The rate of tumor control was 80.7%. No morbidity was observed. There was no correlation between death and the parameters studied. The survival rates and times observed in our study of the patients treated for brain metastases by radiosurgery and overexposed were among the good results of the international literature. Deaths were not related to the overdose and no side effect was noted. This dosimetric accident has not had worse consequences in this population.


Stereotactic radiosurgery for patients with "radioresistant" brain metastases.
Brown PD, Brown CA, Pollock BE, Gorman DA, Foote RL.

Division of Radiation Oncology, Mayo Clinic, Rochester, Minnesota 55905, USA.

OBJECTIVE:
Our aim was to evaluate the efficacy of stereotactic radiosurgery (SRS) for the treatment of patients with brain metastases that have been determined to be "radioresistant" on the basis of histological examination.

METHODS:
We reviewed the medical records of 41 consecutive patients who presented with 83 brain metastases from radioresistant primaries and subsequently underwent SRS. All patients were followed until death or for a median of 31 months after SRS. Tumor histologies included renal cell carcinoma (16 patients), melanoma (23 patients), and sarcoma (2 patients). Eighteen patients (44%) had a solitary metastasis, and 23 patients (56%) had multiple metastases.

RESULTS:
The median overall survival time was 14.2 months after SRS. On the basis of univariate analysis, systemic disease status ($P = 0.006$) and Radiation Therapy Oncology Group recursive partitioning analysis (RPA) class ($P = 0.005$) were associated with survival. The median survival time was 23.5 months for patients in RPA Class I status and 10.5 months for patients in RPA Class II or III status. There was a trend ($P = 0.12$) toward improved median survival for patients with renal cell carcinoma (17.8 mo) as compared with patients with melanoma (9.7 mo). Multivariate analysis
showed RPA class (P = 0.038) and histological diagnosis of primary tumor (P < 0.001) to be independent predictors for overall survival. In the 35 patients who underwent follow-up imaging, 9 (12%) of 73 tumors recurred locally. In 54% of the patients, distant brain failure (DBF) developed. Whole brain radiotherapy (WBRT) improved local control and decreased DBF, according to the univariate and multivariate analyses. Patients who received adjuvant WBRT in addition to SRS had 6-month actuarial local control of 100% as compared with 85% among those who did not receive WBRT (P = 0.018). Patients who received adjuvant WBRT with SRS had a 6-month actuarial DBF rate of 17%, as compared with a rate of 64% among patients who had SRS alone (P = 0.0027).

CONCLUSION:
Well-selected patients with brain metastases from radioresistant primary tumors who undergo SRS survive longer than historical controls. RPA Class I status and primary renal cell carcinoma predict longer survival. Adjuvant WBRT improves local control and decreases DBF but does not affect overall survival. Further studies are needed to determine which patients should receive WBRT.

J Neurosurg. 2006 Oct;105(4):555-60
Gamma knife surgery for metastatic brain tumors from renal cell carcinoma.
Shuto T, Inomori S, Fujino H, Nagano H.
Department of Neurosurgery, Yokohama Rosai Hospital, Yokohama, Kanagawa, Japan.
shuto@yokohamah.rofuku.go.jp

OBJECT:
The authors evaluated the results of Gamma Knife surgery (GKS) for the treatment of metastatic brain tumors from renal cell carcinoma (RCC).

METHODS:
The authors conducted a retrospective review of the clinical characteristics and treatment outcomes in 69 patients with metastatic brain tumors from RCC who underwent GKS at the authors' institution. Fifty-one patients were men, and 18 were women. The mean patient age was 64.2 years (range 45-85 years). The 69 patients underwent a total of 104 GKS procedures for treatment of 314 tumors. Eighteen patients received repeated GKS. Follow-up magnetic resonance (MR) imaging was used at a mean of 7.1 months after GKS to evaluate the change in 132 tumors after treatment. The mean prescription dose at the tumor margin was 21.8 Gy. The tumor growth control rate was 82.6%. Tumor volume and the delivered peripheral dose were significantly correlated with tumor growth control on univariate and multivariate analyses. Sixty (45.5%) of the 132 tumors assessed with MR imaging were associated with apparent peritumoral edema at the time of GKS. After treatment, peritumoral edema disappeared in 27 tumors, decreased in 13, was unchanged in 16, and progressed in four. Newly developed peritumoral edema after GKS was rare. The delivered peripheral dose was
significantly correlated with control of peritumoral edema. The overall median survival time after GKS was 9.5 months. In this study, 34 patients died of systemic disease and 10 died of progressive brain metastases. Multivariate analysis showed that the number of lesions at the first GKS, the Karnofsky Performance Scale score at the first GKS, the recursive partitioning analysis classification, and the interval from diagnosis of RCC to brain metastasis were significantly correlated with survival time.

CONCLUSIONS:
Gamma Knife surgery is effective for metastatic brain tumors from RCC. The disappearance rate of tumors is relatively low, but growth control is high. The delivered dose to the tumor margin is significantly correlated with the control of peritumoral edema. Gamma Knife surgery should be used as the initial treatment modality, if possible, even in patients with multiple metastases. Repeated GKS is recommended for newly developed brain metastases because of the low sensitivity of RCC to conventional radiation therapy.

IMPORTANT


Stereotactic radiosurgery without radiation therapy providing high local tumor control of multiple brain metastases from renal cell carcinoma.
Muacevic A, Kreth FW, Mack A, Tonn JC, Wowra B.

Department of Neurosurgery, Ludwig-Maximilians-University, Klinikum Grosshadern, Munich, Germany.
amuacevi@helios.med.uni-muenchen.de

The aim of this study was to analyse treatment effects after stereotactic radiosurgery (SRS) without whole brain radiation therapy (WBRT) as primary treatment for patients harboring brain metastases of renal cell carcinoma (RCC). During an 8-year period, 85 patients with 376 brain metastases from RCC underwent 134 outpatient SRS procedures. 65 % of all patients had multiple brain metastases. The median tumor volume was 1.2 cm (3) (range: 0.1 - 14.2 cm (3)). Mean prescribed tumor dose was 21.2 (+/- 3.2) Gy. Local/distant tumor recurrences were treated by additional SRS in cases of stable systemic disease. Overall median survival was 11.1 months after SRS. The local tumor control rate after SRS was 94 %. Most patients (78 %) died because of systemically progressing cancer. A KPS > 70 and RTOG class I were related to prolonged survival time. Patients of the RTOG groups I, II and III survived for 24.2 months, 9.2 months and 7.5 months, respectively. There was no permanent morbidity after SRS. 11 patients (12.9 %) showed transient radiogenic complications and 3 patients (3.5 %) died because of intratumoral bleedings after SRS. Stereotactic radiosurgery alone achieves excellent local tumor control rates for patients with small brain metastases from renal cell carcinoma.
Radiosurgery in patients with renal cell carcinoma metastasis to the brain: long-term outcomes and prognostic factors influencing survival and local tumor control.
Sheehan JP, Sun MH, Kondziolka D, Flickinger J, Lunsford LD.

Department of Neurological Surgery, University of Pittsburgh, University of Pittsburgh Medical Center, Presbyterian Hospital, Pittsburgh, Pennsylvania, USA. jps2f@virginia.edu

OBJECT:
Renal cell carcinoma is a leading cause of death from cancer and its incidence is increasing. In many patients with renal cell cancer, metastasis to the brain develops at some time during the course of the disease. Corticosteroid therapy, radiotherapy, and resection have been the mainstays of treatment. Nonetheless, the median survival in patients with renal cell carcinoma metastasis is approximately 3 to 6 months. In this study the authors examined the efficacy of gamma knife surgery in treating renal cell carcinoma metastases to the brain and evaluated factors affecting long-term survival.

METHODS:
The authors conducted a retrospective review of 69 patients undergoing stereotactic radiosurgery for a total of 146 renal cell cancer metastases. Clinical and radiographic data encompassing a 14-year treatment interval were collected. Multivariate analyses were used to determine significant prognostic factors influencing survival. The overall median length of survival was 15 months (range 1-65 months) from the diagnosis of brain metastasis. After radiosurgery, the median survival was 13 months in patients without and 5 months in those with active extracranial disease. In a multivariate analysis, factors significantly affecting the rate of survival included the following: 1) younger patient age (p = 0.0076); 2) preoperative Karnofsky Performance Scale score (p = 0.0012); 3) time from initial cancer diagnosis to brain metastasis diagnosis (p = 0.0017); 4) treatment dose to the tumor margin (p = 0.0252); 5) maximal treatment dose (p = 0.0127); and 6) treatment isodose (p = 0.0354). Prior tumor resection, chemotherapy, immunotherapy, or whole-brain radiation therapy did not correlate with extended survival. Postradiosurgical imaging of the brain demonstrated that 63% of the metastases had decreased, 33% remained stable, and 4% eventually increased in size. Two patients (2.9%) later underwent a craniotomy and resection for a tumor refractory to radiosurgery or a new symptomatic metastasis. Eighty-three percent of patients died of progression of extracranial disease.

CONCLUSIONS:
Stereotactic radiosurgery for treatment of renal cell carcinoma metastases to the brain provides effective local tumor control in approximately 96% of patients and a median length of survival of 15 months. Early detection of brain metastases, aggressive treatment of systemic disease, and a therapeutic strategy including radiosurgery can offer patients an extended survival.
Int J Urol. 2002 Nov;9(11):618-25; discussion 626; author reply 627

Gamma-knife radiosurgery for brain metastasis of renal cell carcinoma: results in 42 patients.

Department of Urology, Tohoku University School of Medicine, Aobaku, Sendai, Japan.
hoshi@uro.med.tohoku.ac.jp

BACKGROUND:
The present study provides data from clinical experience with gamma-knife radiosurgery (GK) in patients with brain metastasis from renal cell carcinoma (RCC) and shows the value of this less invasive treatment modality.

METHODS:

Forty-two patients received GK. Twenty of the 42 cases had multiple brain metastases. Extracranial metastases were observed in the lung (38 cases), bone (12 cases), liver (9 cases), lymph node (5 cases) and skin (6 cases).

RESULTS:
Neurological symptoms seen in 40 patients were rapidly improved after GK in 32 patients (80%). Magnetic resonance imaging (MRI) evaluation after GK in 32 patients showed the disappearance of brain tumor in 9 patients (28%). Complete response was obtained by GK in tumors up to 30 mm in diameter. Repeated GK for newly developed lesions was conducted in 11 patients. Extracranial tumor resection was conducted in 7 cases (lung: 3, skin: 2, liver: 1, adrenal: 1). Chemo-radiotherapy or immunotherapy was effective in 8 cases (lung: 5, liver: 2, bone: 1). The actual one-, two- and three-year survival rates were 44.9%, 16.8%, and 11.2%, respectively. The median survival time was 12.5 months. In univariate analysis, the patients with successfully treated extracranial metastases had significantly better prognosis. In multivariate analysis, the patients with Karnofsky performance scale (KPS) > or = 80%, who were treated by GK more than once and obtained complete response (CR) or partial response (PR) by GK, had significantly better prognosis.

CONCLUSION:
Gamma-knife radiosurgery for RCC is an effective non-invasive modality of treatment. It offers a high local control rate and an improved quality of life and survival rate.
OBJECT:
The aim of this study was to evaluate the therapeutic profile of repeated gamma knife surgery (GKS) for renal cell carcinoma that has metastasized to the brain on multiple occasions.

METHODS:
Data from this study were culled from a single institution and cover a 6-year period of outpatient radiosurgery. A standard protocol for indication, dose planning, and follow up was established. In cases of distant or local recurrences, radiosurgery was undertaken repeatedly (up to six times in one individual). Seventy-five patients harboring 350 cerebral metastases were treated. Relief from pretreatment neurological symptoms occurred in 72% of patients within a few days or a few weeks after the procedure. The actuarial local tumor control rate after the initial GKS was 95%. In patients free from relapse of intracranial metastases after repeated radiosurgery, long-term survival was 91% after 4 years; median survival was 11.1+/-3.2 months after radiosurgery and 4.5+/-1.1 years after diagnosis of the primary kidney cancer. Survival following radiosurgery was independent of patient age and sex, side of the renal cell carcinoma, pretreatment of the cerebrum by using radiotherapy or surgery, number of brain metastases and their synchronization with the primary renal cell carcinoma, and the frequency of radiosurgical procedures. In contrast, survival was dependent on the patient's clinical performance score and the extracranial tumor status. Tumor bleeding was observed in seven patients (9%) and late radiation toxicity (LRT) in 15 patients (20%). Treatment-related morbidity was moderate and mostly transient. Late radiation toxicity was encountered predominantly in long-term survivors.

CONCLUSIONS:
Outpatient repeated radiosurgery is an effective and only minimally invasive treatment for multiple brain metastases from renal cell cancer and is recommended as being the method of choice to control intracranial disease, especially in selected patients with limited extracranial disease. Physicians dealing with such patients should be aware of the characteristic aspects of LRT.

Stereotactic radiosurgery for brain metastasis from renal cell carcinoma.

Mori Y, Kondziolka D, Flickinger JC, Logan T, Lunsford LD.

Department of Neurosurgery, the Center for Image-Guided Neurosurgery, University of Pittsburgh, Pennsylvania, USA.

BACKGROUND:
The authors evaluated results after stereotactic radiosurgery (SR) for brain metastases from renal cell carcinoma (RCC) and identified factors associated with improved survival and tumor control.

METHODS:
The authors reviewed the management results from a total of 52 RCC brain metastases in 35 consecutive patients who underwent stereotactic radiosurgery (SR) during a 9-year interval. Twenty-eight patients also underwent whole brain radiation therapy (WBRT). The mean tumor volume was 2.4 mL (range, 0.1-14.1 mL). The mean dose delivered to the tumor margin was 17 gray (Gy) (range, 13-20 Gy). Univariate and multivariate testing was performed to determine significant prognostic factors.

RESULTS:
The median survival was 11 months after SR and 14 months after brain tumor diagnosis.

Only 2 patients (8%) died of progression of the irradiated tumor. Age < 55 years, lack of active systemic disease, and use of chemotherapy and/or immunotherapy after SR were significant favorable prognostic factors in multivariate testing. Post-SR imaging was evaluated in 26 patients (39 tumors).

The local control rate from the 39 treated tumors imaged was 90% (tumor disappearance, 21%; tumor regression, 44%; and stable disease, 26%). Local recurrence developed in 3 patients (4 lesions) and remote brain disease in 12 patients. No patient developed a new focal neurologic deficit due to SR. Patients were classified into two groups: SR with and SR without WBRT. The addition of WBRT to SR did not improve survival. Distant failure occurred similarly in both groups (46% vs. 50%). WBRT combined with SR may contribute to local control, but did not prevent the development of new remote tumors.

CONCLUSIONS:
SR for brain metastasis from RCC results in brain disease control in the majority of patients and was associated with few complications. Early detection of brain metastases and treatment with SR provides extended quality survival.
FRACTIONATED WHOLE BRAIN RADIOTHERAPY

External radiation of brain metastases from renal carcinoma: a retrospective study of 119 patients from the M. D. Anderson Cancer Center.
Wróński M, Maor MH, Davis BJ, Sawaya R, Levin VA.

Department of Neuro-Oncology Research, Staten Island University Hospital, NY, USA.

PURPOSE:
Approximately 10% of patients with metastatic renal cell carcinoma are diagnosed with brain metastases. Most of these patients receive palliative radiotherapy and die of progressive brain metastatic disease. This retrospective study examines the M. D. Anderson Cancer Center experience with such patients who received only whole brain radiation therapy (WBRT).

METHODS AND MATERIALS:
Records of 200 patients with brain metastases from renal carcinoma who were treated at M. D. Anderson Cancer Center between 1976 and 1993 were reviewed. Of these patients, 119 received WBRT only and constitute the basis of this study. Different prognostic factors were analyzed.

RESULTS:
Overall median survival time from diagnosis of the brain metastases was 4.4 months. Multiple brain tumors were treated in 70 patients (58.8%) who had a survival of 3.0 months compared with 4.4 months for patients having a single brain metastasis (p = 0.043). Among 117 patients the causes of death were neurologic in 90 (76%), systemic cancer in 19 (16%), and unknown in 9 (8%). Survival rates at 6 months, 1 year, and 2 years, were 33.6, 16.8, and 5.9%, respectively. Patients in whom brain metastases were diagnosed synchronously with a renal primary (n = 24) had a median survival time of 3.4 months compared with 3.2 months for those 95 who were diagnosed metachronously (p < 0.79, NS). In the Cox multivariate analysis of 13 possible prognostic factors, only a single brain metastasis (p = 0.0329), lack of distant metastases at the time of diagnosis (p = 0.0056), and tumor diameter < or = 2 cm (p < 0.0016) were statistically significant.

CONCLUSION:
These unsatisfactory results with WBRT suggest that more aggressive approaches, such as surgery or radiosurgery should be applied whenever possible.
2.d. Brain Metastases from Malignant Melanoma

Various series after Gamma Knife radiosurgery of malignant melanoma demonstrate reproducible local tumour control rates between 77 and 90% and a short-term local control rate of 98% at 3 months (Grob 1998). The median survival was 23.5 months for patients in RPA Class I and 10.5 months for patients in RPA Class II or III in a combined group of patients with brain metastases of melanoma and renal cell carcinoma (Brown 2008). When Gamma Knife radiosurgery was the initial treatment of intracranial melanoma metastases, patients in RPA Class I survived a median of 14.5 months, compared with a median survival of 5 months for patients in RPA Class II or III (Radbill 2004).

References (Gamma Knife in the Treatment of Metastases from Malignant Melanoma)


Selected Literature 1998-2011: Brain Metastases from Malignant Melanoma

World Neurosurg. 2011 May-Jun;75(5-6):684-91; discussion 598-603.

Gamma knife surgery in brain melanosomas: absence of extracranial metastases and tumor volume strongest indicators of prolonged survival.

Skeie BS, Skeie GO, Enger PØ, Ganz JC, Heggdal JI, Ystevik B, Hatteland S, Parr E, Pedersen PH.

Department of Neurosurgery, Haukeland University Hospital, Norway. bsai@helse-bergen.no

OBJECTIVE:

To review a series of patients who underwent Gamma Knife surgery (GKS) to identify prognostic factors for local growth control and survival.

METHODS:
During the period 1996-2006, 77 patients (42 men and 35 women) with a total of 143 metastases underwent GKS. A solitary lesion was present in 40 patients (51.9%).

RESULTS:
Growth control was achieved in 114 of 128 (89.1%) tumors and 59 of 70 (84.3%) patients. The median survival was 7 months (range 0-73 months) after GKS and 67 months (range 4-327 months) from the time of diagnosis. Patients with absence of extracranial disease lived longer than patients with more widespread disease—median 16 months (range 3-52 months) versus 6 months (range 0-73 months; P = 0.014). A total tumor volume of less than 5 cc was associated with longer survival (P = 0.041). Survival was significantly longer in recursive partitioning analysis (RPA) class 1 (22 months) than RPA class 2 (7 months) and RPA class 3 (3 months; P = 0.008). Even in cases of treatment failure with tumor growth or appearance of new metastases, GKS slowed down the cerebral disease with no significant reduction in the duration of survival.

CONCLUSIONS:
GKS for melanoma brain metastasis provides a high rate of local tumor control. Survival is longest for well-functioning patients with absence of extracranial metastases or with an intracerebral total tumor volume less than 5 cc.

IMPORTANT: LARGE SERIES
Outcome predictors of Gamma Knife surgery for melanoma brain metastases. Clinical article.
Liew DN, Kano H, Kondziolka D, Mathieu D, Niranjan A, Flickinger JC, Kirkwood JM, Tarhini A, Moschos S, Lunsford LD.

Department of Neurological Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.

OBJECT:
To evaluate the role of stereotactic radiosurgery (SRS) in the management of brain metastases from melanoma, the authors assessed clinical outcomes and prognostic factors for survival and tumor control.

METHODS:
The authors reviewed 333 consecutive patients with melanoma who underwent SRS for 1570 brain metastases from cutaneous and mucosal/acral melanoma. The patient population consisted of 109 female and 224 male patients with a median age of 53 years. Two hundred eleven patients (63%) had multiple metastases. One hundred eighteen patients (35%) underwent whole-brain radiation therapy (WBRT). The target volume ranged from 0.1 cm(3) to 37.2 cm(3). The median marginal dose was 18 Gy.
RESULTS:
Actuarial survival rates were 70% at 3 months, 47% at 6 months, 25% at 12 months, and 10% at 24 months after radiosurgery. Factors associated with longer survival included controlled extracranial disease, better Karnofsky Performance Scale score, fewer brain metastases, no prior WBRT, no prior chemotherapy, administration of immunotherapy, and no intratumoral hemorrhage before radiosurgery. The median survival for patients with a solitary brain metastasis, controlled extracranial disease, and administration of immunotherapy after radiosurgery was 22 months. Sustained local tumor control was achieved in 73% of the patients. Sixty-four (25%) of 259 patients who had follow-up imaging after SRS had evidence of delayed intratumoral hemorrhage. Sixteen patients underwent a craniotomy due to intratumoral hemorrhage. Seventeen patients (6%) had asymptomatic and 21 patients (7%) had symptomatic radiation effects. Patients with ≤ 8 brain metastases, no prior WBRT, and the recursive partitioning analysis Class I had extended survivals (median 54.3 months).

CONCLUSIONS:
Stereotactic radiosurgery is an especially valuable option for patients with controlled systemic disease even if they have multiple metastatic brain tumors.

J Neurosurg. 2008 Dec;109 Suppl:122-8
Gamma Knife surgery in the management of radioresistant brain metastases in high-risk patients with melanoma, renal cell carcinoma, and sarcoma.
Department of Radiation Oncology, State University of New York Upstate Medical University, Syracuse, New York 13210, USA.

OBJECT:
The purpose of this study was to examine the results of using Gamma Knife surgery (GKS) for brain metastases from classically radioresistant malignancies.

METHODS:
The authors retrospectively reviewed the records of 76 patients with melanoma (50 patients), renal cell carcinoma (RCC; 23 patients), or sarcoma (3 patients) who underwent GKS between August 1998 and July 2007. Overall patient survival, intracranial progression, and local progression of individual lesions were analyzed.
RESULTS:
The median age of the patients was 57 years (range 18-85 years) and median Karnofsky Performance Scale (KPS) score was 80 (range 20-100). Sixty-two patients (81.6%) had uncontrolled extracranial disease. A total of 303 intracranial lesions (average 3.97 per patient, range 1-27 lesions) were treated using GKS. More than 3 lesions were treated in 30 patients (39.5%). Median GKS tumor margin dose was 18 Gy (range 8-30 Gy). Thirty-seven patients (48.7%) underwent whole brain radiation therapy.

The actuarial 12-month rate for freedom from local progression for individual lesions was 77.7% and was significantly higher for RCC compared with melanoma (93.6 vs 63.0%; p = 0.001). The percentage of coverage of the prescribed dose to target volume was the only treatment-related variable associated with local control: 12-month actuarial rate of freedom from local progression was 71.4% for lesions receiving \( \geq 90\% \) coverage versus 0.0% for lesions receiving < 90% (p = 0.00048). Median overall survival was 5.1 months after GKS and 8.4 months after the discovery of brain metastases. Univariate analysis revealed that KPS score (p = 0.000004), recursive partitioning analysis class (p = 0.00043), and single metastases (p = 0.028), but not more than 3 metastases, to be prognostic factors of overall survival. The KPS score remained significant after multivariate analysis. Overall survival for patients with a KPS score \( \geq 70 \) was 7.1 months compared with 1.3 months for a KPS score \( \leq 60 \) (p = 0.013).

CONCLUSIONS:
Gamma Knife surgery is an effective treatment option for patients with radioresistant brain metastases. In this setting, KPS score appeared to be a more important factor in predicting survival than having > 3 metastases. Higher rates of local tumor control were achieved for RCC in comparison with melanoma, and this may have an effect on survival in some patients. Although outcomes generally remained poor in this study population, these results suggest that GKS can be considered as a treatment option for many patients with radioresistant brain metastases, even if these patients have multiple lesions.

Neurosurgery. 2008 Feb;62 Suppl 2:790-801
Stereotactic radiosurgery for patients with "radioresistant" brain metastases.
Brown PD, Brown CA, Pollock BE, Gorman DA, Foote RL.
Division of Radiation Oncology, Mayo Clinic, Rochester, Minnesota 55905, USA.

OBJECTIVE:
Our aim was to evaluate the efficacy of stereotactic radiosurgery (SRS) for the treatment of patients with brain metastases that have been determined to be "radioresistant" on the basis of histological examination.

METHODS:
We reviewed the medical records of 41 consecutive patients who presented with 83 brain metastases from radioresistant primaries and subsequently underwent SRS. All patients were followed until death or for a median of 31 months after SRS. Tumor histologies included renal cell carcinoma (16 patients), melanoma (23 patients), and sarcoma (2 patients). Eighteen patients (44%) had a solitary metastasis, and 23 patients (56%) had multiple metastases.

RESULTS:
The median overall survival time was 14.2 months after SRS. On the basis of univariate analysis, systemic disease status (P = 0.006) and Radiation Therapy Oncology Group recursive partitioning analysis (RPA) class (P = 0.005) were associated with survival. The median survival time was 23.5 months for patients in RPA Class I status and 10.5 months for patients in RPA Class II or III status. There was a trend (P = 0.12) toward improved median survival for patients with renal cell carcinoma (17.8 mo) as compared with patients with melanoma (9.7 mo). Multivariate analysis showed RPA class (P = 0.038) and histological diagnosis of primary tumor (P < 0.001) to be independent predictors for overall survival. In the 35 patients who underwent follow-up imaging, 9 (12%) of 73 tumors recurred locally. In 54% of the patients, distant brain failure (DBF) developed. Whole brain radiotherapy (WBRT) improved local control and decreased DBF, according to the univariate and multivariate analyses. Patients who received adjuvant WBRT in addition to SRS had 6-month actuarial local control of 100% as compared with 85% among those who did not receive WBRT (P = 0.018). Patients who received adjuvant WBRT with SRS had a 6-month actuarial DBF rate of 17%, as compared with a rate of 64% among patients who had SRS alone (P = 0.0027).

CONCLUSION:
Well-selected patients with brain metastases from radioresistant primary tumors who undergo SRS survive longer than historical controls. RPA Class I status and primary renal cell carcinoma predict longer survival. Adjuvant WBRT improves local control and decreases DBF but does not affect overall survival. Further studies are needed to determine which patients should receive WBRT.

Gamma knife radiosurgery in the management of malignant melanoma brain metastases.
Mathieu D, Kondziolka D, Cooper PB, Flickinger JC, Niranjan A, Agarwala S, Kirkwood J, Lunsford LD.
Department of Neurological Surgery, University of Pittsburgh, School of Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania 15213, USA.

OBJECTIVE:
Radiosurgery is increasingly used to manage malignant melanoma brain metastases. We reviewed our series of patients who underwent radiosurgery for melanoma brain metastases to assess clinical outcomes and identify prognostic factors for survival and cerebral disease control.
METHODS:
Two hundred forty-four patients had radiosurgery for the management of 754 metastatic tumors. A mean of 2.6 tumors were irradiated per procedure. The median tumor volume was 4.4 cm³. The median margin and maximum doses used were 18 and 32 Gy, respectively.

RESULTS:
The median survival was 5.3 months after radiosurgery (mean, 10 mo; range, 0.2-114.3 mo). Patients survived a median of 7.8 months (mean, 13.4 mo) from the diagnosis of brain metastases and 44.9 months (mean, 69 mo) after the diagnosis of the primary tumor. Survival was better in patients with controlled systemic disease (12.7 mo), single brain metastasis (6.8 mo), and a Karnofsky performance score of 90 or 100% (6.3 mo). Sustained local control was achieved in 86.2% of tumors. Increased tumor volume and previous evidence of hemorrhage increased the risk of local failure. Multiple lesions and failure to provide systemic immunotherapy were predictors for the occurrence of new brain metastases, which developed in 41.7% of the patients. Symptomatic radiation changes occurred in 6.6% of the patients. Overall, 71.4% of the patients improved or remained clinically stable. Brain disease was the cause of death in 40.5% of the patients, usually from the development of new metastases.

CONCLUSION:
Gamma knife radiosurgery for malignant melanoma brain metastases is safe and effective and provides a high rate of durable local control. Improved survival can be achieved in patients with single metastasis, controlled systemic disease, and a high Karnofsky performance score.

Neurosurg Focus. 1998 Jun 15;4(6):e1
Outcomes in patients treated with gamma knife radiosurgery for brain metastases from malignant melanoma.
Friehs GM, Legat J, Zheng Z, Pendl G, Noren GC.

Department of Clinical Neurosciences (Neurosurgery), Brown University, Providence, Rhode Island; and Department of Neurosurgery, Karl-Franzens University, Graz, Austria.

In order to determine the effectiveness of gamma knife (GK) radiosurgery in patients with malignant melanoma metastases, the authors conducted a prospective multicenter study. Forty-five patients with a total of 96 lesions were treated and followed to measure survival time, tumor control rate, and Karnofsky Performance Scale (KPS) score. The mean survival time was 8.7 months (median 4.2 months), and tumor control was achieved in 86% of lesions. When obtained, the median preoperative KPS of 80 was maintained at a median of 80 post-GK treatment. The authors found GK treatment for metastases of malignant melanoma to be highly effective in controlling tumor growth.
Survival rates obtained after GK treatment were found to be superior to historically obtained data concerning external beam radiotherapy follow up. Radiosurgery with the GK can therefore be considered a good primary treatment option for metastatic brain disease of malignant melanoma.


Gamma-Knife radiosurgery in the management of melanoma patients with brain metastases: a series of 106 patients without whole-brain radiotherapy.


Dermatology Department, Hôpital Sainte Marguerite, Marseille, France. marqueste@wanadoo.fr

**PURPOSE:**

To assess retrospectively a strategy that uses Gamma-Knife radiosurgery (GKR) in the management of patients with brain metastases (BM) of malignant melanoma (MM).

**METHODS:**

GKR without whole-brain radiotherapy (WBRT) was performed for patients with Karnofsky Performance Status (KPS) of 60 or above who harbored 1 to 4 BMs of 30 mm or less and was repeated as often as needed. Survival was assessed in the whole population, whereas local-control rates were assessed for patients with follow-up longer than 3 months.

**RESULTS:**

A total of 221 BMs were treated in 106 patients; 61.3% had a single BM. Median survival from the time of GKR was 5.09 months. Control rate of treated BMs was 83.7%, with 14% of complete response (14 BMs), 42% of partial response (41 BMs), and 43% of stabilization (43 BMs). In multivariate analysis, survival prognosis factors retained were KPS greater than 80, cortical or subcortical location, and Score Index for Radiosurgery (SIR) greater than 6. On the basis of KPS, BM location, and age, a score called MM-GKR, predictive of survival in our population, was defined.

**CONCLUSION:**

Gamma-Knife radiosurgery provides a surgery-like ability to obtain control of a solitary BM and could be considered as an alternative treatment to the combination of GKR+WBRT as a palliative strategy. MM-GKR classification is more adapted to MM patients than are SIR, RPA and Brain Score for Brain Metastasis.

**Melanoma Res. 2006 Feb;16(1):51-7**
Integration of gamma knife surgery in the management of cerebral metastases from melanoma.
Christopoulou A, Retsas S, Kingsley D, Paddick I, Lindquist C.

Oncology Centre, Cromwell Hospital, London, UK.

The aim of this study was to investigate the effect of gamma knife surgery on the local control of cerebral metastases from melanoma and to assess survival. In 29 patients, 105 of 178 cerebral metastases were treated with gamma knife surgery. Only five patients had metastases confined to the brain. Of the 96 metastases with magnetic resonance imaging follow-up, 61.5% regressed by more than 50% of the pretreatment volume, 25% regressing by more than 90% and 13.5% completely. The median survival from gamma knife surgery was 5.7 months (longest survival, 38 months). In multivariate analyses, a larger number of lesions requiring treatment (P < 0.001), recursive partitioning analysis class (P = 0.009) and a long time interval from initial melanoma diagnosis to detection of cerebral metastases (P = 0.001) influenced survival. It can be concluded that gamma knife surgery is a useful adjunct in the management of cerebral metastases from melanoma and has a significant impact on local control. Its greatest potential may be achieved in conjunction with systemic chemotherapy, especially in the presence of extracerebral metastases.

Gamma Knife radiosurgery for intracranial metastatic melanoma: an analysis of survival and prognostic factors.

Division of Radiation Oncology, Arthur G. James Cancer Hospital and Research Institute, The Ohio State University, Columbus, OH, USA. mkoc@atauni.edu.tr

Objective of this study was to evaluate retrospectively the effectiveness of Gamma Knife radiosurgery for intracranial metastatic melanoma and to identify prognostic factors related to survival. Twenty-six patients with intracranial metastases (72 lesions) from melanoma underwent Gamma Knife radiosurgery. In 14 patients (54%) whole-brain radiotherapy (WBRT) was performed as part of the initial treatment, and in 12 patients (38%) immunotherapy and/or chemotherapy was given after Gamma Knife radiosurgery. The median tumor volume for Gamma Knife radiosurgery treated lesions was 1.72 cm3. The median prescribed radiation dose was 18 Gy (range 8-22 Gy) typically prescribed to the isodose at the tumor margin. Univariate and multivariate analyses were used to determine significant prognostic factors affecting survival. Overall median survival was 6 months after Gamma Knife radiosurgery, and 1-year survival was 25%. The median survival from the onset of brain metastases was 9 months and from the original diagnosis of melanoma was 50 months (range 4-160 months). There were no major acute or late GKS complications. In univariate testing, the Karnofsky score equal to or higher than 90% (P < 0.01, log-rank test), supratentorial localization (P < 0.001, log-
rank test), intracranial tumor volume less than 1 cm³ (P < 0.02, log-rank test), and absence of neurological signs or symptoms before Gamma Knife radiosurgery (P < 0.003, log-rank test) were significant favorable factors for survival. In multivariate regression analyses, the most important predictors associated with increased survival were a KPS > or = 90 (P < 0.023), female sex (P < 0.004), supratentorial localization (P < 0.01), and absence of neurological symptoms (P < 0.008). Radiosurgery is a noninvasive, safe, and effective treatment option for patients with single or multiple intracranial metastases from melanoma. Female sex, Karnofsky score > or = 90, supratentorial localization and lack of symptoms before the Gamma Knife radiosurgery were good independent predictors of survival.

A comparison of survival rates for treatment of melanoma metastatic to the brain.
Stone A, Cooper J, Koenig KL, Golfinos JG, Oratz R.
New York University School of Medicine, New York, New York 10029, USA. anne.stone@mssm.edu

INTRODUCTION:
A retrospective review of 91 patients with brain metastases from malignant melanoma treated at New York University Medical Center between 1989-1999. Overall survival was the outcome evaluated.

METHODS: Charts of 91 patients having malignant melanoma with brain metastases were reviewed. Cases were stratified according to therapy: surgical excision, surgical excision plus whole brain radiation therapy, gamma knife stereotactic radiosurgery, gamma knife stereotactic radiosurgery plus whole brain radiation therapy, and whole brain radiation therapy alone. Patients treated with gamma knife stereotactic radiosurgery plus radiation therapy were combined with patients treated with surgical excision plus radiation therapy and compared to those treated with radiation therapy alone. Prognostic characteristics of the two groups were compared and survival curves were generated using the Kaplan-Meier method. The Cox proportional hazards model was used to control for prognostic factors that differed between the groups.

RESULTS:
Patients treated with gamma knife stereotactic radiosurgery or surgical excision plus radiation therapy were younger, less likely to present with symptoms, and presented with fewer metastases to the brain than patients treated with radiation therapy alone. A survival benefit of 7.3 months (p = 0.05) was found to be associated with gamma knife radiosurgery or surgical excision plus radiation therapy over radiation therapy alone after controlling for differences in age, number of brain lesions, and presence of symptoms.

DISCUSSION:
This retrospective study of 91 patients treated for melanoma metastases to the brain attempts to examine the effectiveness of different treatments in prolonging survival. Our results suggest that surgical excision or stereotactic radiosurgery with gamma knife in addition to radiation therapy may be more effective than radiation alone at prolonging survival for patients with a limited number of brain lesions.

CONCLUSION:
Survival of patients with melanoma metastases to the brain may be prolonged by treatment with gamma knife stereotactic radiosurgery or surgical excision plus whole brain radiation therapy.

Initial treatment of melanoma brain metastases using gamma knife radiosurgery: an evaluation of efficacy and toxicity.
Radbill AE, Fiveash JF, Falkenberg ET, Guthrie BL, Young PE, Meleth S, Markert JM.
Department of Medicine, Children's Hospital, Boston, Massachusetts, USA.

BACKGROUND:
Melanoma is the primary malignancy that is most likely to metastasize to the brain. Because such an event carries an almost uniformly poor prognosis, the current study reviewed outcomes and identified associated prognostic indicators for 51 consecutive patients receiving gamma knife (GK) radiosurgery in the initial treatment of 188 intracranial melanoma metastases.

METHODS:
Data were collected retrospectively from a single-center GK radiosurgery database and from primary patient medical records and radiographs.

RESULTS:
At presentation, 71% of patients had multiple intracranial metastases, and extracranial metastases were present in 66% of patients. Thirty-two patients (63%) were initially treated with GK radiosurgery alone, whereas the remainder received GK radiosurgery in combination with surgery and/or whole-brain radiotherapy (WBRT). Overall median survival from time of GK radiosurgery was 26 weeks. Subgroup analysis revealed a median survival of 77 weeks for patients presenting with a single lesion, compared with 20 weeks for patients presenting with multiple lesions (P = 0.003). Patients in recursive partitioning analysis (RPA) Class I survived a median of 57 weeks, compared with a median survival of 20 weeks for patients in RPA Class II or III (P = 0.002). Although long-term imaging follow-up revealed that a majority of patients experienced distant brain metastases, multivariate analysis showed that distant metastases occurred significantly sooner in patients with extracranial metastases (P = 0.0004). Addition of initial WBRT had no significant effect on the time to development of new brain metastases (P = 0.13). Local control (crude) was
observed in 81% of lesions initially treated with GK. Patients experienced improved or stable symptoms for a median of 37 weeks post-GK radiosurgery.

CONCLUSIONS:
Survival analyses supported the use of GK radiosurgery in the initial treatment of patients with melanoma brain metastases, with best results occurring in patients presenting with a single lesion.
Gamma knife radiosurgery for intracranial metastatic melanoma: a 6-year experience.

Department of Neurological Surgery, Wayne State University, Detroit, Michigan 48201, USA.

OBJECT:
The purpose of this study was to evaluate retrospectively the effectiveness of stereotactic radiosurgery for intracranial metastatic melanoma and to identify prognostic factors related to tumor control and survival that might be helpful in determining appropriate therapy.

METHODS:
Twenty-four patients with intracranial metastases (115 lesions) metastatic from melanoma underwent radiosurgery. In 14 patients (58.3%) whole-brain radiotherapy (WBRT) was performed, and in 12 (50%) chemotherapy was conducted before radiosurgery. The median tumor volume was 4 cm³ (range 1-15 cm³). The mean dose was 16.4 Gy (range 13-20 Gy) prescribed to the 50% isodose at the tumor margin. All cases were categorized according to the Recursive Partitioning Analysis classification for brain metastases. Univariate and multivariate analyses of survival were performed to determine significant prognostic factors affecting survival. The mean survival was 5.5 months after radiosurgery. The analyses revealed no difference in terms of survival between patients who underwent WBRT or chemotherapy and those who did not. A significant difference (p < 0.05) in mean survival was observed between patients receiving immunotherapy or those with a Karnofsky Performance Scale (KPS) score of greater than 90.

CONCLUSIONS:
The treatment with systemic immunotherapy and a KPS score greater than 90 were factors associated with a better prognosis. Radiosurgery for melanoma-related brain metastases appears to be an effective treatment associated with few complications.

Survival by radiation therapy oncology group recursive partitioning analysis class and treatment modality in patients with brain metastases from malignant melanoma: a retrospective study.
Buchsbaum JC, Suh JH, Lee SY, Chidel MA, Greskovich JF, Barnett GH.

Department of Radiation Oncology, The Cleveland Clinic Foundation, Cleveland, Ohio 44195, USA.

BACKGROUND:
In a population of patients with brain metastases from melanoma, the authors sought to determine whether various therapies provided any benefit at all, whether local therapy was better than whole brain radiotherapy (WBRT), and whether combined local therapy and WBRT provided any advantage over local therapy alone. They also analyzed survival according to a Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) to determine how well the RTOG RPA classes predicted survival in this patient population and whether treatments varied in effectiveness from category to category.

METHODS:
A total of 74 patients with brain metastases from melanoma were treated at The Cleveland Clinic Foundation between 1984 and 1998. For this study, the authors reviewed patient charts and confirmed survival status. Survival was compared by treatment modality (surgical resection, WBRT, stereotactic radiosurgery, or WBRT combined with local therapy). Survival also was compared according to the RTOG RPA prognostic classes (Class 1, Class 2, or Class 3), which has not been validated previously in patients with malignant melanoma.

RESULTS:
The median survival was 5.5 months for all patients. Survival varied significantly by RTOG prognostic class; The median survival was 10.5 months (range, 2.2-99.2 months) for patients in Class 1, 5.9 months (range, 0.2-43.9 months) for patients in Class 2, and 1.8 months (range, 0.1-6.9 months) for patients in Class 3 (P < 0.0001). Survival analysis showed that combined treatment offered significantly better survival (P < 0.0001; combined vs. other). The median survival was 8.8 months (range, 1.8-99.2 months) for the combined therapy group, 4.8 months (range, 1.2-27.8 months) for the local therapy alone group, 2.3 months (range, 0.2-9.6 months) for the WBRT alone group, and 1.1 months (0.1-3.0 months) for the group that received no therapy.

CONCLUSIONS:
Adding WBRT to local therapy may improve survival in this group of patients: Combined therapy was superior to WBRT alone. The RPA classification scheme likely has prognostic value for patients with brain metastases from malignant melanoma. Prospective studies are required to overcome selection bias and confirm these results.

Metastatic melanoma to the brain: prognostic factors after gamma knife radiosurgery.
Yu C, Chen JC, Apuzzo ML, O'Day S, Giannotta SL, Weber JS, Petrovich Z.

Department of Radiation Oncology, University of Southern California Keck School of Medicine, Los Angeles, CA 90033, USA. chengyu@hsc.usc.edu

PURPOSE:
To identify important prognostic factors predictive of survival and tumor control in patients with metastatic melanoma to the brain who underwent gamma knife radiosurgery.

METHODS AND MATERIALS:
A total of 122 consecutive patients with 332 intracranial melanoma metastases underwent gamma knife radiosurgery over a 5-year period. Of these, 39 (32%) also received whole-brain irradiation (WBI). The median tumor volume was 0.8 cm$^3$ (range: 0.02-30.20 cm$^3$), and the median prescribed dose was 20 Gy (range: 14-24 Gy). Median follow-up was 6.8 months. Univariate and multivariate analyses of survival and freedom from progression were performed using the following parameters: status of systemic disease, intracranial tumor volume, number of lesions, tumor location, Karnofsky performance status, gender, age, and WBI.

RESULTS:
Overall median survival was 7.0 months from time of radiosurgery and 9.1 months from the onset of brain metastasis. In multivariate analysis, improved survival was noted in patients with total intracranial tumor volume $<$ 3 cm$^3$ ($p = 0.003$) and inactive systemic disease ($p = 0.0065$), whereas other parameters studied were of lesser importance (tumor location, $p = 0.056$, and Karnofsky performance status, $p = 0.086$), or of no significance (number of lesions, WBI, age, and gender). Freedom from subsequent brain metastasis depended on intracranial tumor volume ($p = 0.0018$) and status of systemic disease ($p = 0.034$).

CONCLUSIONS:
Stereotactic radiosurgery is an effective treatment modality for patients with intracranial metastatic melanoma. Tumor volume and status of systemic disease are good independent predictors of survival and freedom from tumor progression.

Gamma surgery for melanoma metastases in the brain.
Mingione V, Oliveira M, Prasad D, Steiner M, Steiner L.
Lars Leksell Center for Gamma Surgery, Department of Neurological Surgery, University of Virginia, Charlottesville 22908, USA.

OBJECT:
The aim of this study was to evaluate the usefulness and limitations of gamma surgery (GS) in the treatment of brain metastases from melanoma.

METHODS:
Imaging and clinical outcomes in 45 patients treated for 92 brain metastases from melanoma between October 1989 and October 1999 were retrospectively analyzed. Follow-up imaging
studies were available in 35 patients with 66 treated lesions. Twenty-four percent of the lesions disappeared, 35% shrank, 23% remained unchanged, and 18% increased in size. No undue radiation-induced changes were observed in the surrounding brain. Clinical data were available in all patients. No deaths or neurological morbidity related to GS was observed. The median survival time, calculated using the Kaplan-Meier method, was 10.4 months from the time of GS. In both univariate and multivariate Cox regression analyses, a single brain lesion and lack of visceral metastases were statistically predictive of a better prognosis. Six of eight patients with solitary metastasis (that is, a single brain metastasis with no primary visceral tumor) were still alive at the close of the study, none of them with disease progression, with a follow-up period ranging between 14 and 82 months. Sixteen patients in this series received adjunctive whole-brain radiation therapy, which had no impact on their survival time or local and distant control of the brain disease.

CONCLUSIONS:
Gamma surgery is effective in treating melanoma metastases in the brain. It appears that the radiobiology of a single high dose overcomes the radioresistance barrier, yielding better results than fractionated radiation.

Neurosurgery. 1999 Jan;44(1):59-64; discussion 64-6
Gamma knife radiosurgery for metastatic melanoma: an analysis of survival, outcome, and complications.

Department of Neurological Surgery, University of Southern California School of Medicine, Los Angeles 90033, USA.

OBJECTIVE:
Although the mainstays for treatment of metastatic brain disease have been surgery and/or external beam radiation therapy, an increasing number of patients are being referred for stereotactic radiosurgery as the primary intervention for their intracranial pathological abnormalities. The lack of efficacy and cognitive and behavioral consequences of whole brain irradiation have prompted clinicians to select patients for alternative therapies. This study analyzes the effectiveness of Leksell gamma unit therapy for metastatic melanoma to the brain.

METHODS:
We present our experience with 59 Leksell gamma unit treatment sessions in 45 consecutive patients who presented with metastatic melanoma to the brain. Five of these procedures were performed as salvage therapy for patients who needed second radiosurgical treatment for new lesions that were remote from the previous targets and were not included in the overall analyses.
RESULTS:
The population included 78% male patients. The mean patient age was 53 years (age range, 24-80 yr). The mean time from diagnosis of primary melanoma to discovery of brain metastasis was 43 months (median, 27.5 mo; range, 1-180 mo). At the time of diagnosis of brain disease, 35.5% of the patients (16 of 45 patients) had neurological symptoms, 77.7% (35 of 45 patients) had known visceral metastases, and 11.1% (5 of 45 patients) had seizure disorders. Eighty-six percent of the lesions (80 of 93 lesions) were cortical, 12% (11 of 93 lesions) were cerebellar, 1% (1 of 93 lesions) were pontine, and 1% (1 of 93 lesions) were thalamic. Fifty-seven percent of the sessions (31 of 54 sessions) were performed for a single lesion, 24.1% (13 of 54 sessions) for two lesions, 9.2% (5 of 54 sessions) for three lesions, 7.4% (4 of 54 sessions) for four lesions, and 1.8% (1 of 54 sessions) for five lesions. The mean treatment volume was 5.6 cc, with a mean prescription of 21.6 Gy to the 56.0% mean isodose line. The median survival time of the patients in our population, using Kaplan-Meier curves, was 43 months from the time of diagnosis of primary melanoma (range, 3-180 mo) and 8 months (range, 1-20 mo) from the time of gamma knife treatment. Complications included seizures within 24 hours of the procedure in four patients, with transient nausea and vomiting in three patients, transient worsening of preprocedure paresis responsive to steroids in three patients, and increased confusion in one patient. All 45 patients were located for follow-up (mean follow-up duration, 1 yr). After gamma knife treatment, 78% of the patients (35 of 45 patients) experienced either improved or stable neurological symptomatology before death or at the time of the latest follow-up examination. There were 26 deaths (58%). The cause of death was determined to be neurological in only 2 of 45 patients (7.7%). Follow-up magnetic resonance images revealed a 97% local tumor control rate of gamma knife-treated lesions, with 28% radiographic disappearance (9 of 32 cases). Six patients developed new lesions remote from radiosurgical targets and underwent second procedures.

CONCLUSION:
Although metastatic melanoma to the brain continues to have a foreboding prognosis for long-term survival, gamma knife radiosurgery seems to be a relatively safe, noninvasive, palliative therapy, halting or reversing neurological progression in 77.8% of treated patients (35 of 45 patients). The survival rate matches or exceeds those previously reported for surgery and other forms of radiotherapy. Only 7.7% of the patients in our study population who died as a result of metastatic melanoma (2 of 26 patients) died as a result of neurological disease. The routine use of therapeutic level antiseizure medication is emphasized, considering the findings of our review.
Stereotactic radiosurgery for cerebral metastatic melanoma: factors affecting local disease control and survival.
Mori Y, Kondziolka D, Flickinger JC, Kirkwood JM, Agarwala S, Lunsford LD.

Department of Neurological Surgery, Center for Image-Guided Neurosurgery, University of Pittsburgh Cancer Institute, University of Pittsburgh, PA 15213, USA.

PURPOSE:
The development of a brain metastasis represents an ominous event for patients with malignant melanoma. We evaluated results after stereotactic radiosurgery (SR) for patients with metastatic melanoma to identify patient outcomes and factors for survival.

METHODS:
The authors reviewed the management results of 60 consecutive patients with melanoma metastases, with a total of 118 melanoma brain metastases, undergoing SR during a 9-year interval. Of these, 51 also had whole-brain radiation therapy (WBRT). A total of 118 tumors of mean volume of 2.95 ml (range, 0.1-25.5 ml) were treated by SR with a mean margin dose of 16.4 Gy (range, 10 to 20 Gy). Univariate and multivariate analyses were used to determine significant prognostic factors affecting survival in 60 patients.

RESULTS:
Median survival was 7 months after SR in all 60 patients and 10 months from brain tumor diagnosis (mean follow-up period, 9.3 months). Lack of active systemic disease and a solitary metastasis were associated with improved survival in multivariate analysis (median, 15 months). The imaging-defined local control rate of evaluable tumors (n = 72) was 90% (disappearance = 11%, shrinkage = 44%, and stable = 35%). Local recurrence developed in 7 patients and remote brain disease developed in 14 patients. WBRT combined with radiosurgery did not improve survival nor local tumor control. New brain metastases developed less often when WBRT was added to SR (23% vs. 44%), but this difference was not significant. Only 4 patients (7%) died from progression of a radiosurgery-managed tumor. No patient developed a delayed radiation-related complication, but 3 patients developed delayed intratumoral hemorrhage at the radiosurgery site, 2 of whom had new symptoms.

CONCLUSIONS:
Stereotactic radiosurgery for melanoma brain metastasis is effective and is associated with few complications. The use of radiosurgery alone is an appropriate management strategy for many patients with solitary tumors.
Gamma knife radiosurgery for malignant melanoma brain metastases.

Department of Radiation Oncology, University of California, San Francisco 94143-0226, USA.

PURPOSE:
To evaluate the efficacy and toxicity of gamma knife radiosurgery in the treatment of melanoma metastases to the brain.

PATIENTS AND METHODS:
We retrospectively reviewed 55 patients with single or multiple intracranial melanoma metastases treated at the University of California, San Francisco, with gamma knife radiosurgery from 1991 through 1995. Sixteen patients were treated with gamma knife radiosurgery for recurrence following previous radiation therapy, 11 received radiosurgery as a boost to whole-brain radiation therapy, and 28 had radiosurgery alone for initial management of brain metastases. The median minimum radiosurgery tumor dose for 140 treated lesions was 19 Gy (range, 10-22 Gy) prescribed at the 35% to 90% isodose contour (median, 50%). The median total target volume per patient was 6.1 cc (range, 0.25-28.3 cc).

RESULTS:
With a median follow-up of 75 weeks in living patients, the median survival times were 35 weeks overall: 35 weeks for patients with solitary metastases versus 33 weeks for those with multiple metastases. A factor that was significant in univariate analysis of survival was total target volume treated. This parameter remained significant on multivariate analysis. The actuarial median freedom from progression analyzed by lesion for 113 lesions in 46 patients with imaging follow-up was 89 weeks with 6-month and 1-year actuarial freedom from progression rates of 89% (95% confidence interval, 80%-95%) and 77% (95% confidence interval, 62%-87%). In univariate analysis, improved freedom from progression was associated with smaller target volume treated, smaller maximum diameter, or higher prescribed dose. Four patients (7%) developed acute Radiation Therapy Oncology Group grade > or = 2 morbidity, and five patients (9%) developed late grade > or = 2 morbidity.

DISCUSSION:
Median survival and freedom from progression in patients treated with radiosurgery for melanoma metastatic to the brain are comparable to results in published radiosurgery series of grouped histologies. For melanoma patients, total intracranial tumor volume appears to be of greater prognostic significance than the absolute number of metastases treated. We conclude that gamma knife radiosurgery is effective and should be considered among various management strategies.
2.e. Brain Metastases from Colo-rectal Carcinoma

Local tumor control was achieved in 84% and 96% in colorectal cancer metastases undergoing Gamma Knife radiosurgery. The addition of WBRT to radiosurgery did not improve survival and local tumor control rates (Hasegawa 2003, Schoeggl 2002).

References (Gamma Knife in the Treatment of Metastases from Colo-rectal Carcinoma)

Selected Literature 2002-2012: Brain Metastases from Colo-rectal Carcinoma

World Neurosurg. 2012 Apr 16.
Skeie BS, Enger PO, Ganz JC, Skeie GO, Parr E, Hatteland S, Ystevik B, Heggdal JI, Pedersen PH.
Department of Neurosurgery, Haukeland University Hospital, Bergen, Norway; Department of Surgical Science, Haukeland University Hospital, Bergen, Norway.

OBJECTIVE:
There are few reports on the effect of gamma knife surgery (GKS) for brain metastases from colorectal cancer. The purpose of this study was to identify prognostic factors for local control, complications, and survival in our series of patients treated with GKS.

METHODS:
Eighty patients (36 males, 44 females) with 140 metastases who received GKS between 1996 and 2008 were retrospectively reviewed. The mean tumor volume was 6.13 (0.01-35.5) cm$^3$; the prescription dose was 21.1 (10-25.1) Gy and the maximum dose 42.7 (17.2-66.7) Gy; and the tumor cover was 95.0% (72%-100%).

RESULTS:
Growth control was achieved in 93 of 121 tumors (76.9%) and 42 of 68 (61.8%) patients, while treatment failure was seen in 28 of 121 tumors (23.1%). Local control was better if a high
prescription dose of 25 Gy was used, 88.4% vs. 71.4% (P = 0.017), or if tumor volume was <5 cm(3) (86.4%), compared with 69.9% for 5-20 cm(3) and 51.9% for >20 cm(3) (P = 0.002). The hazard ratio for local failure with lower prescription doses was 2.8 (P = 0.026) in the unadjusted, and 8.5 (P = 0.055) in the adjusted multivariate analysis (tumor volumes >5 cm(3)). The median survival was 6 months (range 0-75) after GKS. Age <70 years (P < 0.001) and high RPA class (P = 0.032) were associated with longer survival. Fifteen patients (22.1%) had persistent edema on follow-up MRI, possibly because of radiation damage to the tumor. Radiation-induced edema was asymptomatic in 93.8%. We found neither a decrease in the incidence of new metastases nor improved survival when whole-brain radiation therapy was given prior to GKS.

CONCLUSIONS:
GKS provides reasonable local tumor control. Local control rate is highest if the margin dose is 25 Gy and the tumor volume <5 cm(3). Radiation edema was common but rarely symptomatic. Survival is longest for young, well-functioning patients.

The efficacy of gamma knife radiosurgery for advanced gastric cancer with brain metastases.
Park YS, Chang JH, Chang JW, Park YG.
Department of Neurosurgery, Gamma Knife Clinic, Severance Hospital, Brain Research Institute, Yonsei University College of Medicine, 134, Shinchon-dong, Seodaemoon-gu, Seoul 120-752, Republic of Korea.

Abstract
The aim of this study was to retrospectively investigate the efficacy of gamma knife radiosurgery for brain metastases from advanced gastric cancer (AGC) comparing whole brain radiotherapy (WBRT). Between January 1991 and May 2008, 56 patients with brain metastases from AGC, treated with GKR or WBRT, were reviewed to assess prognostic factors affecting survival. Most brain metastases were diagnosed based on MRI, both metachronous and synchronous brain metastases, adenocarcinoma and signet ring carcinoma were included, but excluded cases of gastric lymphoma. Fifteen patients with a median age of 54.0 years (range, 42-67 years) were treated with GKR: 11 were treated with GKR only, 2 with surgery plus GKR, 1 with repeated GKR, 1 with GKR plus WBRT, and the other 1 with WBRT plus GKR. Forty-one were treated with WBRT only. The median number of metastatic brain lesions was 3 (range, 1-15), and treatment involved 17.0 Gy (range 14-23.6 Gy), or 30 Gy with fractionated radiotherapy. The median survival after brain metastases for GKR treatment was 40.0 weeks [95% confidence interval (CI) 44.9-132.1 weeks] and WBRT was 9.0 weeks 95% CI, 8.8-21.9 weeks). The progression free survival of 15 GKR treated patients was 56.5 weeks (95% CI 33.4-79.5 weeks). The recursive partitioning analysis (RPA) (class 2 vs. class 3) and use of GKR were correlated with prolonged survival in univariate and multivariate analyses. Age, sex, pathology, leptomeningeal seeding, tumor size (≥3 cm), extracranial metastases, single metastasis, chemotherapy, and synchronous metastases
were not correlated with a good prognosis in both univariate and multivariate analysis. Based on our study, the use of GKR and RPA class 2 resulted in more favorable clinical outcomes in patients with brain metastases from AGC.


Gamma knife surgery for 1-10 brain metastases without prophylactic whole-brain radiation therapy: analysis of cases meeting the Japanese prospective multi-institute study (JLGK0901) inclusion criteria. Serizawa T, Hirai T, Nagano O, Higuchi Y, Matsuda S, Ono J, Saeki N.

Tokyo Gamma Unit Center, Tsukiji Neurological Clinic, Tokyo, Japan. gamma-knife.serizawa@nifty.com

We evaluated the results of stereotactic radiosurgery (SRS) alone using gamma knife (GK) for selected patients with 1-10 brain metastases without prophylactic whole-brain radiation therapy (WBRT) among JLGK0901-eligible cases. Seven hundred seventy-eight consecutive cases meeting the following JLGK0901 study inclusion criteria were analyzed: (1) newly diagnosed brain metastases, (2) 1-10 brain lesions, (3) less than 10 cm(3) volume of the largest tumor, (4) less than 15 cm(3) total tumor volume, (5) no magnetic resonance (MR) findings of cerebrospinal fluid (CSF) dissemination, and (6) no impaired activity of daily living [<70 Karnofsky Performance Score (KPS)] due to extracranial disease. At initial treatment, all lesions were irradiated with SRS without upfront WBRT. Thereafter, enhanced magnetic resonance imaging (MRI) was applied every 2-3 months, and new distant lesions were appropriately retreated with SRS or WBRT. We divided patients according to tumor number: single lesion for group A (280 cases), 2 for group B (135), 3-4 for group C (148), 5-6 for group D (93), and 7-10 for group E (122). Differences among groups were compared in terms of overall, neurological, qualitative, and new-lesion-free survival (NLFS). Median age was 65 years (range 26-92 years). There were 505 men and 273 women. The primary organ was lung in 579 patients, gastrointestinal tract in 79, breast in 48, urinary tract in 34, and others/unknown in 38. Mean survival time was 0.72 years (0.83 years for 1, 0.69 years for 2, 0.69 years for 3-4, 0.59 years for 5-6, and 0.62 years for 7-10 metastases). On multivariate analysis, significant poor prognostic factors for overall survival (OS) were active systemic disease, poor (<70) initial KPS, and male gender. Neurological survival and qualitative survival at 1 year were 92.7% and 88.2%, respectively. NLFS at 6 months and 1 year were 69.8% and 43.8%, respectively. There were statistically significant differences in new lesion emergence between groups A and B and between groups B and C. SRS using GK provides excellent results in selected patients with 1-10 brain lesions, without prophylactic WBRT. This study revealed that brain lesion number has no effect on any of the four types of survivals, which is anticipated to be confirmed by the JLGK0901 study.
OBJECT:
The outcomes after Gamma Knife surgery (GKS) were retrospectively analyzed in patients with brain metastases from radioresistant primary colorectal cancer to evaluate the efficacy of GKS and the prognostic factors for local tumor control and overall survival.

METHODS:
The authors reviewed the medical records of 152 patients with 616 tumors. The group included 102 men and 50 women aged 35-85 years (mean age 64.4 years), who underwent GKS for metastatic brain tumors from colorectal cancer between April 1992 and September 2008 at Yokohama Rosai Hospital.

RESULTS:
The mean prescription dose to the tumor margin was 18.5 Gy (range 8-30 Gy). The mean tumor volume at GKS was 2.0 cm(3) (range 0.004-10.0 cm(3)). The primary tumors were located in the colon in 88 patients and the rectum in 64. The median interval between the diagnosis of primary lesions and the diagnosis of brain metastases was 27 months (range 0-180 months). The median neuroradiological follow-up period after GKS was 3 months (mean 6.4 months, range 1-93 months). The local tumor growth control rate, based on MR imaging, was 91.2%. The significant factors for unfavorable local tumor growth control, based on multivariate analysis, were larger tumor volume (p = 0.001) and lower margin dose (p = 0.016). The median overall survival time was 6 months. Lower Karnofsky Performance Scale (KPS) score (p = 0.026) and the presence of extracranial metastases (p = 0.004) at first GKS were significantly correlated with poor overall survival period in multivariate analysis. The cause of death was systemic disease in 112 patients and neurological disease in 13 patients. Leptomeningeal carcinomatosis was significantly correlated with a shorter duration of neurological survival in multivariate analysis (p < 0.0001).

CONCLUSIONS:
Gamma Knife surgery is effective for suppression of local tumor growth in patients with brain metastases from radioresistant colorectal primary cancer. Therefore, clinical and radiological screening of intracranial metastases for patients with lower KPS scores and/or the presence of extracranial metastases as well as follow-up examinations after GKS for brain metastases should be performed periodically in patients with colorectal cancer, because the neurological prognosis is improved by initial
and repeat GKS for newly diagnosed or recurrent tumors leading to a prolonged high-quality survival period.

**J Neurosurg. 2009 Sep;111(3):423-30.**
Gamma Knife surgery for brain metastases from gastrointestinal cancer.
Da Silva AN, Nagayama K, Schlesinger DJ, Sheehan JP.

The Lars Leksell Gamma Knife Center, Department of Neurological Surgery, University of Virginia Health System, Charlottesville, Virginia 22908, USA.

**OBJECT:**
Brain metastases from gastrointestinal cancers are rare. However, the incidence is increasing because patients with gastrointestinal carcinoma tend to live longer due to earlier diagnosis and more effective treatment of systemic disease. The purpose of this study was to evaluate the efficacy of Gamma Knife surgery (GKS) for the treatment of brain metastases from gastrointestinal cancers.

**METHODS:**
The authors performed a retrospective review of 40 patients (18 women and 22 men) who had undergone GKS to treat a total of 118 metastases from gastrointestinal cancers between January 1996 and December 2006. The mean patient age was 58.7 years, and the mean Karnofsky Performance Scale (KPS) score was 70. There were 7 patients with esophageal cancer, 25 with colon cancer, 5 with rectal cancer, 2 with pancreatic cancer, and 1 with gastric cancer. Nineteen patients were treated with whole-brain radiotherapy and/or local brain radiotherapy before GKS. Twenty-four patients had extracranial metastases, and 3 had an additional primary cancer. The mean metastatic brain tumor volume was 4.3 cm³, and the mean maximum tumor dose varied from 17.1 to 76.7 Gy (mean 41.8 Gy).

**RESULTS:**
Follow-up imaging studies were available in 25 patients with a total of 90 treated metastases. The results demonstrate a tumor control rate of 91%. The median survival time was 6.7 months, and the 6-month and 1-year survival rates were 55 and 25%, respectively. A univariate analysis revealed that the KPS score (<or=70 vs >or=80) was significant (p=0.018) for improved survival.

**CONCLUSIONS:**
Results in this series suggest that GKS can be an effective tool for the treatment of brain metastases from gastrointestinal cancer.
Stereotactic radiosurgery for brain metastases from gastrointestinal tract cancer.
Hasegawa T, Kondziolka D, Flickinger JC, Lunsford LD.
Surg Neurol. 2003 Dec;60(6):506-14; discussion 514-5

Department of Neurological Surgery, Pittsburgh, Pennsylvania 15213, USA.

BACKGROUND:
Outcomes in patients with brain metastases from gastrointestinal tract cancers are not well defined. In this study we used precise, single-session, focal tumor irradiation (radiosurgery) in patients with brain metastases and evaluated the results.

METHODS:
Thirty-nine patients had brain metastases from gastrointestinal tract cancer and were treated with radiosurgery. Thirty-two also had whole brain radiotherapy. Primary lesions included colorectal cancer (n = 25), esophageal cancer (n = 11), cholangiocarcinoma (n = 1), duodenal cancer (n = 1), and jejunal cancer (n = 1). Seventy-two tumors were treated.

RESULTS:
The overall median survival was 9 months after diagnosis of metastatic brain disease and 5 months after radiosurgery. The 1-year survival rate after radiosurgery was 19%. The last imaging study of 49 tumors showed complete remission (CR) in 3 tumors (6.1%), partial remission (PR) in 27 tumors (55.1%), no change (NC) in 11 tumors (22.4%), and progression in 8 tumors (16.3%). The local tumor control rate (CR, PR, NC) was 84%. Two patients (5.1%) had a new or worsening neurologic deficit after radiosurgery.

CONCLUSIONS:
Stereotactic radiosurgery provides reasonable local control of brain metastases from gastrointestinal tract cancer with few side effects. However, it should be used judiciously in patients with active extracranial cancers since the expected survival may be limited.
Stereotactic radiosurgery for brain metastases from colorectal cancer.
Schoeggl A, Kitz K, Reddy M, Zauner C.

Department of Neurosurgery, University of Vienna, Austria.

PURPOSE:
The development of brain metastases represents an ominous event for patients with colorectal cancer. We evaluated results following stereotactic radiosurgery (SR) for patients with metastatic colorectal cancer to identify efficacy of SR and prognostic factors for survival.

METHODS:
This is a retrospective study of 60 brain metastases from colorectal cancer in 35 consecutive patients who underwent SR from January 1993 to December 1996. Thirteen patients also underwent additional whole-brain radiation therapy (WBRT). The median dose delivered to the tumor margin was 20 Gray (range 16-28 Gy), in most cases the tumor enclosing the 50% isodose (range 40-60%). Patients were classified into two groups: SR with and SR without WBRT. Univariate and multivariate testing was performed to determine significant prognostic factors.

RESULTS:
The median survival time was 6 months after SR and 40 months after diagnosis of primary tumor. A Karnofsky performance scale >70 was a significantly favorable prognostic factor in univariate and multivariate testing. Post-SR imaging was evaluated in 32 patients and in 54 cerebral lesions. Local tumor control was revealed in 94% of patients and 96% of treated tumors. Two patients developed local recurrences, and remote brain disease was revealed in five. No patient experienced a new focal neurologic deficit due to SR. The addition of WBRT to SR did not improve survival and local tumor control rates. Distant control rate was borderline in univariate analysis and significantly improved for patients who received additional WBRT in multivariate analysis.

CONCLUSION:
SR for brain metastases from colorectal cancer results in a high local tumor control rate of 94% associated with few complications and therefore provides patients with a higher quality of their remaining life.
Quality of Life and Treatment of Brain Metastases

Patients receiving stereotactic radiosurgery alone were at significantly lower risk of a significant decline in learning and memory function by 4 months when compared to patients undergoing additional WBRT (Chang 2009). The conclusion from this study was interpreted as level 1 evidence to support the use of stereotactic radiosurgery alone. Fractionated cranial irradiation causes a negative impact on health-related quality of life scales particularly due to fatigue and hair loss (Slotman 2009) and causes cognitive dysfunction immediately after the beginning of radiotherapy and subacute radiation effects on verbal memory function that are observed in both therapeutic and prophylactic cranial irradiation patients (Welzel 2008). These effects were more pronounced in patients with above-average performance at baseline (Welzel 2008). Delayed significant CNS toxicity 72 months after fractionated radiotherapy is a known phenomenon (Doyle 2008). It was shown in a smaller prospective study after Gamma Knife treatment for brain metastases that quality of life parameters remained either unchanged or improved in patients who had no evidence of intracranial or extracranial tumor progression (DiBiase 2002). Quality of life was analysed as part of the prospective randomised analysis RTOG 9508. At 6 months follow-up a statistically significant improvement in clinical performance and decreased steroid use was found in the stereotactic radiosurgery boost treatment group when compared with the patients who had been treated by fractionated radiotherapy only (Andrews 2004).

References (Quality of Life and Treatment of Brain Metastases)


patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet May 22;363(9422):1665-72

Selected Literature: Quality of Life and Treatment of Brain Metastases

Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial.

Source
Department of Radiation Oncology, The University of Texas, M D Anderson Cancer Center, Houston, TX, USA. echang@mdanderson.org

Abstract
BACKGROUND:
It is unclear whether the benefit of adding whole-brain radiation therapy (WBRT) to stereotactic radiosurgery (SRS) for the control of brain-tumours outweighs the potential neurocognitive risks. We proposed that the learning and memory functions of patients who undergo SRS plus WBRT are worse than those of patients who undergo SRS alone. We did a randomised controlled trial to test our prediction.

METHODS:
Patients with one to three newly diagnosed brain metastases were randomly assigned using a standard permuted block algorithm with random block sizes to SRS plus WBRT or SRS alone from Jan 2, 2001, to Sept 14, 2007. Patients were stratified by recursive partitioning analysis class, number of brain metastases, and radioresistant histology. The randomisation sequence was masked until assignation, at which point both clinicians and patients were made aware of the treatment allocation. The primary endpoint was neurocognitive function: objectively measured as a significant deterioration (5-point drop compared with baseline) in Hopkins Verbal Learning Test-Revised (HVLT-R) total recall at 4 months. An independent data monitoring committee monitored the trial using Bayesian statistical methods. Analysis was by intention-to-treat. This trial is registered at www.ClinicalTrials.gov, number NCT00548756.

FINDINGS:
After 58 patients were recruited (n=30 in the SRS alone group, n=28 in the SRS plus WBRT group), the trial was stopped by the data monitoring committee according to early stopping rules on the basis that
there was a high probability (96%) that patients randomly assigned to receive SRS plus WBRT were significantly more likely to show a decline in learning and memory function (mean posterior probability of decline 52%) at 4 months than patients assigned to receive SRS alone (mean posterior probability of decline 24%). At 4 months there were four deaths (13%) in the group that received SRS alone, and eight deaths (29%) in the group that received SRS plus WBRT. 73% of patients in the SRS plus WBRT group were free from CNS recurrence at 1 year, compared with 27% of patients who received SRS alone ($p=0.0003$). In the SRS plus WBRT group, one case of grade 3 toxicity (seizures, motor neuropathy, depressed level of consciousness) was attributed to radiation treatment. In the group that received SRS, one case of grade 3 toxicity (aphasia) was attributed to radiation treatment. Two cases of grade 4 toxicity in the group that received SRS alone were diagnosed as radiation necrosis.

**INTERPRETATION:**

Patients treated with SRS plus WBRT were at a greater risk of a significant decline in learning and memory function by 4 months compared with the group that received SRS alone. Initial treatment with a combination of SRS and close clinical monitoring is recommended as the preferred treatment strategy to better preserve learning and memory in patients with newly diagnosed brain metastases.


Memory function before and after whole brain radiotherapy in patients with and without brain metastases.


**Source**

Department of Radiation Oncology, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany.

**Abstract**

**PURPOSE:**

To prospectively compare the effect of prophylactic and therapeutic whole brain radiotherapy (WBRT) on memory function in patients with and without brain metastases.

**METHODS AND MATERIALS:**

Adult patients with and without brain metastases ($n = 44$) were prospectively evaluated with serial cognitive testing, before RT ($T_0$), after starting RT ($T_1$), at the end of RT ($T_2$), and 6-8 weeks ($T_3$) after RT completion. Data were obtained from small-cell lung cancer patients treated with prophylactic cranial irradiation, patients with brain metastases treated with therapeutic cranial irradiation (TCI), and breast cancer patients treated with RT to the breast.

**RESULTS:**
Before therapy, prophylactic cranial irradiation patients performed worse than TCI patients or than controls on most test scores. During and after WBRT, verbal memory function was influenced by pretreatment cognitive status \( p < 0.001 \) and to a lesser extent by WBRT. Acute (T1) radiation effects on verbal memory function were only observed in TCI patients \( p = 0.031 \). Subacute (T3) radiation effects on verbal memory function were observed in both TCI and prophylactic cranial irradiation patients \( p = 0.006 \). These effects were more pronounced in patients with above-average performance at baseline. Visual memory and attention were not influenced by WBRT.

**CONCLUSIONS:**
The results of our study have shown that WBRT causes cognitive dysfunction immediately after the beginning of RT in patients with brain metastases only. At 6-8 weeks after the end of WBRT, cognitive dysfunction was seen in patients with and without brain metastases. Because cognitive dysfunction after WBRT is restricted to verbal memory, patients should not avoid WBRT because of a fear of neurocognitive side effects.

**Int J Radiat Oncol Biol Phys. 2008 Apr 1;70(5):1361-4.**
Delayed effects of whole brain radiotherapy in germ cell tumor patients with central nervous system metastases.
Doyle DM, Einhorn LH.

**Source**
Department of Medicine, Division of Hematology and Oncology, Indiana University, Indianapolis, IN 46202, USA. dpeoni@iupui.edu

**Abstract**

**PURPOSE:**
Central nervous system (CNS) metastases are uncommon in patients with germ cell tumors, with an incidence of 2-3%. CNS metastases have been managed with whole brain radiotherapy (WBRT) and concomitant cisplatin-based combination chemotherapy. Our previous study did not observe serious CNS toxicity (Int J Radiat Oncol Biol Phys 1991;22:17-22). We now report on 5 patients who developed delayed significant CNS toxicity.

**PATIENTS AND METHODS:**
We observed 5 patients with delayed CNS toxicity. The initial diagnosis was between 1981 and 2003. All patients had poor-risk disease according to the International Germ Cell Consensus Collaborative Group criteria. Of the 5 patients, 3 had CNS metastases at diagnosis and 2 developed relapses with CNS metastases. These 5 patients underwent WBRT to 4,000-5,000 cGy in 18-28 fractions concurrently with cisplatin-based chemotherapy.

**RESULTS:**
All 5 patients developed delayed symptoms consistent with progressive multifocal leukoencephalopathy. The symptoms included seizures, hemiparesis, cranial neuropathy, headaches, blindness, dementia, and ataxia. The median time from WBRT to CNS symptoms was 72 months (range, 9-228). Head imaging revealed multiple abnormalities consistent with gliosis and diffuse cerebral atrophy. Of the 5 patients, 3 had progressive and 2 stable symptoms. Treatment with surgery and/or steroids had modest benefit. The progressive multifocal leukoencephalopathy resulted in significant debility in all 5 patients, resulting in death (3 patients), loss of work, steroid-induced morbidity, and recurrent hospitalizations.

**CONCLUSION:**
Whole brain radiotherapy is not innocuous in young patients with germ cell tumors and can cause late CNS toxicity.

Influence of gamma knife radiosurgery on the quality of life in patients with brain metastases.
DiBlase SJ, Chin LS, Ma L.

**Source**
Departments of Radiation Oncology, University of Maryland Medical Center, Baltimore, Maryland 21201, USA.

**Abstract**
Quality of life (QOL) is an important issue in the treatment of patients with brain metastases. With median survival times often less than 4 months, less invasive treatment options that maximize QOL parameters are essential. In recent years, stereotactic radiosurgery (SRS) has been commonly used as a noninvasive alternative to surgical resection for such patients. This prospective study was undertaken to evaluate QOL in patients undergoing SRS for brain metastases. Between 1999 and 2000, 20 patients with metastatic disease to the brain were evaluated and treated in our Gamma Knife unit. All patients performed the Spitzer QOL survey (10-point scale) both before stereotactic radiosurgery and at each follow-up visit. Primary sites of disease included lung (n = 10), breast (n = 5), melanoma (n = 2), thyroid (n = 1), uterine (n = 1), and kidney (n = 1). Fifteen (75%) had prior whole brain radiotherapy (median dose: 35 Gy). The median age and Karnofsky Performance Status were 58 years and 80, respectively. The median Spitzer score before SRS was 9 (range: 7-10), and the median follow-up time of the patients in this series was 7 months. The median posttreatment Spitzer score at 1 and 3 months after SRS was 9 (range: 5-10) and 8 (range: 4-10), respectively. Crude intracranial tumor control in this cohort of patients was 90%. Extracranial tumor progression was noted in 8 patients (40%), and in these patients, Spitzer scores tended to decrease in value. In those patients who had no evidence of intracranial or extracranial tumor progression, Spitzer scores remained either unchanged or improved.

**Gamma knife SRS is an appropriate treatment modality for maintaining QOL parameters in**
patients with brain metastases. Tumor progression both intracranially and extracranially influences QOL parameters. Confirmation of this finding will require further investigation.

Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial.

Source
Department of Neurosurgery, Thomas Jefferson University Hospital, Philadelphia, PA 19107, USA.
david.andrews@jefferson.edu

Abstract
BACKGROUND:
Brain metastases occur in up to 40% of all patients with systemic cancer. We aimed to assess whether stereotactic radiosurgery provided any therapeutic benefit in a randomised multi-institutional trial directed by the Radiation Therapy Oncology Group (RTOG).

METHODS:
Patients with one to three newly diagnosed brain metastases were randomly allocated either whole brain radiation therapy (WBRT) or WBRT followed by stereotactic radiosurgery boost. Patients were stratified by number of metastases and status of extracranial disease. Primary outcome was survival; secondary outcomes were tumour response and local rates, overall intracranial recurrence rates, cause of death, and performance measurements.

FINDINGS:
From January, 1996, to June, 2001, we enrolled 333 patients from 55 participating RTOG institutions--167 were assigned WBRT and stereotactic radiosurgery and 164 were allocated WBRT alone. Univariate analysis showed that there was a survival advantage in the WBRT and stereotactic radiosurgery group for patients with a single brain metastasis (median survival time 6.5 vs 4.9 months, p=0.0393). Patients in the stereotactic surgery group were more likely to have a stable or improved Karnofsky Performance Status (KPS) score at 6 months' follow-up than were patients allocated WBRT alone (43% vs 27%, respectively; p=0.03). By multivariate analysis, survival improved in patients with an RPA class 1 (p<0.0001) or a favourable histological status (p=0.0121).

INTERPRETATION:
WBRT and stereotactic boost treatment improved functional autonomy (KPS) for all patients and survival for patients with a single unresectable brain metastasis. WBRT and stereotactic radiosurgery should, therefore, be standard treatment for patients with a single unresectable brain metastasis and considered for patients with two or three brain metastases.

**Gamma Knife in the Treatment of Multiple Brain Metastases**

The local tumour control after the Gamma Knife treatment is not influenced by the total number of brain metastases. In addition, there is increasing evidence for the efficacy of radiosurgery even for patients with multiple (>4) brain metastases. Patients with 3-6 brain metastases treated by Gamma Knife radiosurgery had an actuarial 2-year tumor control rate of 74.3% (Jawahar 2005). Kim analysed the prognostic factors for patient survival and local control of brain metastases after gamma knife radiosurgery and showed that patients with a single lesion survived significantly longer than those with multiple lesions in the univariate analysis, but without statistical significance in the multivariate analysis. The numbers of metastases were not statistically significant parameters for prognosis in this study, but Karnofsky score, tumor volume, controlled primary cancer, and absence of extracranial metastases were associated with longer survival (Kim 2000).

A large group of 183 patients with non-melanoma brain metastases showed that the number of brain metastases was not significantly related to survival (Yan 2003). An earlier study from the same institution had shown that the presence of multiple metastases was associated with a worse survival rate in a univariate analysis without being a significant factor in multivariate analysis (Shu 1996). In Gamma Knife treated patients with breast cancer (Amendola 2000) and renal cancer (Goyal 2000) the survival was independent of the number of the treated brain metastases. The same result was found in a large Gamma Knife series of 458 consecutive patients with 1-5 brain metastases (Petrovich 2002). KPS and absence of systemic disease were associated with longer survival in a retrospective analysis on 135 patients who had undergone Linac- or Gamma Knife radiosurgery, whereas the number of brain metastases did not have an impact (Chidel 2000). The total tumour volume may have a more important impact on the prognosis, since a total tumor volume > 9 cc was associated with shorter survival (Chen 2000). Although some series indicate a less favourable median survival for patients with more than three (Nam 2005) or more than seven metastases (Bhatnagar 2007), there is no simplistic correlation between the number of metastases and the patient’s prognosis. In 521 patients treated with Gamma Knife radiosurgery, Serizawa found a similar outcome in terms of overall and neurological survival, for patients with few (≤3) and many (4-10) brain metastases (Serizawa 2005).

However, several treatment recommendations including clinical practice guidelines limit the number of brain metastases that can be treated with radiosurgery to a virtually arbitrary number of three or four without consideration of tumour volume. These recommendations are primarily based on level I evidence and hence on the available three randomized studies (Andrews 2004, Chougule 2000, Kondziolka 1999). All of these studies have limited their inclusion criteria for patients with less than 4 metastases and patients with a higher
number of metastases were excluded from analysis. This scientific limitation results in a serious practical problem, since results reflecting the study's exclusion criteria are often confused with negative evidence. As a consequence, the radiosurgical treatment is often declined in patients with 4 or more metastases, despite the possibility of an effective local control. Interestingly, multiple studies show evidence for similar local control rates and no increased side effects after radiosurgery of multiple metastases. So far no alternative and superior therapy exists for these patients.
References (Gamma Knife in the Treatment of Multiple Brain Metastases)


Surg Neurol. 2005 Sep;64(3):207-12.
Role of stereotactic radiosurgery as a primary treatment option in the management of newly diagnosed multiple (3-6) intracranial metastases.

Source
Department of Neurosurgery, Louisiana State University Health Sciences Center in Shreveport, Shreveport, LA 71130, USA. ajawah@lsuhsc.edu

Abstract
OBJECTIVE:
The objective of this study was to assess the role of stereotactic radiosurgery in the management of newly diagnosed multiple intracranial metastases from known primary cancer locations.

METHODS:
Fifty (29 women and 21 men) patients received radiosurgery for newly diagnosed 3 or more metastatic brain tumors. Their mean age was 53 years. Lung cancer was the most common primary cancer (66%).

RESULTS:
Arrest in the growth of irradiated tumors was achieved in 41 (82%) patients. Eight patients (16%) required further intervention for tumors in other brain locations. Mean survival after diagnosis of brain disease was 12 months and the brain disease-controlled period was 19 months. The period of brain disease control prolonged (P=.03) with decreasing tumor volumes (<10 mL). Control of treated tumors positively affected survival after diagnosis of brain disease (P=.0001).

CONCLUSION:
Radiosurgery as an adjuvant improves survival in patients with cancer who have newly diagnosed multiple intracranial metastases by arresting the growth of tumors.
Gamma knife radiosurgery for brain metastases: prognostic factors for survival and local control.
Kim DG, Chung HT, Gwak HS, Paek SH, Jung HW, Han DH.

Source
Department of Neurosurgery, College of Medicine Seoul National University and Clinical Research Institute, Seoul National University Hospital, Korea. gknife@plaza.snu.ac.kr

Abstract
OBJECT:
The authors conducted an analysis of prognostic factors for patient survival and local control of brain metastases after gamma knife radiosurgery.

METHODS:
In the survival analysis, 53 consecutive patients with 121 lesions treated in the last 2 years were examined. Common primary sites were lung (26 patients), kidney (seven), breast (three), and colon (three). Patient age ranged from 28 to 75 years (median 58 years) and the female/male ratio was 1:0.9. The median tumor volume was 2.1 cm3 (range 0.02-45.5 cm3) and the average prescription dose was 15.4 Gy to the 50% isodose. The median follow up was 12 months (range 1-23 months) and the median survival was 46 weeks. Six-month and 1-year survival rates were 63% and 39%, respectively. Karnofsky Performance Scale score, tumor volume, and presence of extracranial disease were statistically significant prognostic factors (p < 0.05) for survival in multivariate analysis. Number of lesions, patient age, and adjuvant whole-brain radiation therapy were not statistically significant. Ninety-one of 121 lesions with follow-up images were included in the local control analysis. The 1-year actuarial local control rate was 48%. In multivariate analysis smaller volume was associated with better control (p = 0.0043), and, control period of renal cell carcinoma was shorter than that of the other tumor types (p = 0.0070).

CONCLUSIONS:
Karnofsky Performance Scale score, tumor volume, controlled primary cancer, and absence of extracranial metastases were associated with longer survival in the present study. For local control, tumor volume was a statistically significant factor.
Number of Brain Metastases Is Not an Important Prognostic Factor for Survival Following Radiosurgery for Newly-Diagnosed Nonmelanoma Brain Metastases.

E.S. Yan,1 P.K. Sneed,1 M.W. McDermott,2,1 S. Kunwar,2 W.M. Wara,1 D.A. Larson1,2

1Radiation Oncology, Univ. of California San Francisco, San Francisco, CA, 2Neurological Surgery, Univ. of California San Francisco, San Francisco, CA

Purpose/Objective:
To evaluate the importance of number of brain metastases as a prognostic factor for survival of patients treated with radiosurgery (RS) for newly-diagnosed nonmelanoma brain metastases. (Many poor-prognosis melanoma patients were treated prior to entry on immunotherapy protocols, with 2-fold shorter survival compared with nonmelanoma patients. Other primary sites were similar to each other in terms of prognosis and prognostic factors).

Materials/Methods:
All 541 adults treated with RS for brain metastases at the University of California San Francisco during 1991–2001 were retrospectively reviewed; 210 patients treated for recurrence after whole brain radiotherapy (WBRT) (133), surgery (17), or both surgery and WBRT (60) were excluded; 45 additional patients who underwent resection of a brain metastasis in conjunction with RS were excluded, and 103 additional melanoma patients were excluded, leaving 183 patients with newly-diagnosed nonmelanoma brain metastases, 115 were managed with RS alone and 68 were managed with RS + upfront whole brain radiotherapy (WBRT); 36 were living (20%) with a median follow-up of 16.9 months, and the median survival time from diagnosis of brain metastases was 14.2 months. Survival was equivalent for patients treated with RS vs. RS + adjuvant WBRT, so these two treatment subsets were combined. Median survival times and 1-year and 18-month survival probabilities with 95% confidence intervals are shown in the table below. There was no significant correlation between the number of brain metastases and total target volume. The multivariate analysis to evaluate number of brain metastases as a prognostic factor was performed adjusting for well-known prognostic factors (age, KPS, primary disease control, and extracranial metastases) and total target volume (which was found to be important on univariate analysis). Number of brain metastases was not significant on univariate analysis (p= 0.64, hazard ratio [HR] =1.03) or multivariate analysis (p =0.90, HR =1.01). Favorable prognostic factors on multivariate analysis included age <65 years (p = 0.034, HR= 1.51), KPS >70 (p = 0.074, HR =0.47), absence of extracranial metastases (p =0.021, HR = 1.51), and smaller total target volume (by quartiles) (p = 0.027, HR = 1.19).

Conclusions:
Number of brain metastases is not an important prognostic factor for survival of patients treated with RS for newly-diagnosed nonmelanoma brain metastases.

**Cancer J Sci Am. 1996 Nov-Dec;2(6):335-42.**
Factors influencing survival after gamma knife radiosurgery for patients with single and multiple brain metastases.

**Source**
Department of Radiation Oncology, University of California, San Francisco, San Francisco, California 94143-0226, USA.

**Abstract**

**PURPOSE:**
Radiosurgery has been reported to yield high local control rates for brain metastases. However, further work is needed to define which subgroups of patients may benefit from this treatment modality.

**PATIENTS AND METHODS:**
We reviewed 116 patients who underwent stereotactic radiosurgery for initial management or recurrence of solitary or multiple brain metastases from September 1991 through December 1994 at the University of California, San Francisco. Survival time and time to local-regional failure were calculated using the Kaplan-Meier method. Univariate and multivariate analyses were performed using the Cox proportional hazards model.

**RESULTS:**
Median survival was 40 weeks from radiosurgery. In multivariate analysis, smaller total tumor volume, absence of extracranial metastases, higher Karnofsky score, and age \( \leq 70 \) had a positive effect on survival. In patients initially managed for brain metastases, the addition of whole brain radiotherapy to radiosurgery had no significant effect on survival. Although the presence of multiple metastases was associated with a significantly worse survival rate in patients initially managed with radiosurgery in univariate analysis, it was not as a significant factor in multivariate analysis. An analysis of patients within this series treated with radiosurgery who would have been eligible for Patchell's study on the role of surgery in the treatment of solitary brain metastasis revealed a favorable median survival of 70 weeks.

**CONCLUSIONS:**
We conclude that radiosurgical treatment of brain metastases results in survival times that compare favorably with the historic experience in patients treated with whole brain radiotherapy alone or with surgical resection. In patients presenting initially with brain metastases, radiosurgery alone may yield survival results equivalent to radiosurgery with whole brain radiotherapy, but intracranial control and
quality of life also need to be evaluated. Also, the presence of multiple brain metastases should not be a contraindication for the use of radiosurgery given the good survival achieved with such patients in this series. Each such case should therefore be evaluated based on other factors such as patient's age, Karnofsky score and systemic disease.

Gamma knife radiosurgery in the treatment of patients with single and multiple brain metastases from carcinoma of the breast.
Amendola BE, Wolf AL, Coy SR, Amendola M, Bloch L.

Source
Miami Neuroscience Center Coral Gables, Florida, USA.

Abstract
PURPOSE:
The purpose of the study was to evaluate the results of gamma knife radiosurgery for treatment of brain metastases from carcinoma of the breast.

MATERIALS AND METHODS:
From December 1993 to July 1998, 68 women with breast carcinoma metastatic to the brain were treated with gamma knife radiosurgery at Miami Neuroscience Center in Coral Gables, Florida. The ages ranged from 25 to 80 years, with a median age of 52 years. Thirty-eight patients had previously received conventional modalities of treatment for brain metastases including whole-brain irradiation. A total of 110 treatments were given to the 68 women to an average of eight tumor sites per patient. Minimum doses ranged from 6 to 25 Gy to the 35% to 85% isodose line, with 95% of the prescribed minimum doses ranging from 15 to 24 Gy. Patients were treated for one to three lesions (n = 26), four to seven lesions (n = 18), and eight or more lesions (n = 24).

RESULTS:
The median overall actuarial survival for the entire group was 7.8 months. The actuarial survival was 32% at 1 year. The median follow-up was 7.8 months. Overall local control by lesion was 94% (485/518 lesions), and average tumor volume was 3.3 cm³. Twenty-seven (40%) of 68 eligible patients survived 1 year, nine (13%) survived 2 years, and two (3%) survived more than 3 years. Fifty-one of 56 documented deaths (91%) were unrelated to brain metastases. In a subgroup of 15 patients with single brain metastases, the average tumor volume was 16.6 cm³, and local control was 73% (11/15 lesions). The 15 patients who died had a median survival of 7.7 months (range, 3 to 45.7 months).

CONCLUSIONS:
Gamma knife radiosurgical treatment of patients with brain metastases from carcinoma of the breast has shifted the question of survival to that of systemic control. There was no radiation-induced
dementia, and a remarkably low incidence of local failure was seen. Survival has been found to be independent of the number of lesions treated.

The role of whole brain radiotherapy and stereotactic radiosurgery on brain metastases from renal cell carcinoma.
Goyal LK, Suh JH, Reddy CA, Barnett GH.

**Source**
Departments of Radiation Oncology, The Cleveland Clinic Foundation, Cleveland, OH 44195, USA.

**Abstract**
**PURPOSE:**
We reviewed our experience with patients who have undergone stereotactic radiosurgery (SRS) for brain metastases secondary to renal cell carcinoma (RCC). Analysis was performed to determine the survival, local control, distant brain failure (DBF), and then to define which tumors may not require upfront whole-brain radiotherapy (WBRT).

**METHODS AND MATERIALS:**
Twenty-nine patients with 66 tumors underwent SRS from 1991 to 1998. Median follow-up from time of brain metastases diagnoses relative to each tumor was 12.5 months and 6.8 months from the time of SRS. Median SRS dose was 1,800 cGy to the 60% isodose line. Three patients had undergone SRS for previously treated tumors.

**RESULTS:**
Median survival time from diagnosis was 10.0 months. Overall survival was not affected by age, addition of WBRT, number of lesions, tumor volume, or the presence of systemic disease. Of the 23 patients with follow-up neuroimaging, 4 of 47 (9%) tumors recurred. The addition of WBRT did not improve local control. Of the 13 patients who presented with a single lesion, 3 went on to develop DBF (23%), while 6 of the 10 patients who presented with multiple metastases developed DBF (60%).

**CONCLUSION:**
Patients with brain metastases secondary to RCC treated by SRS alone have excellent local control. The decision of whether or not to add WBRT to SRS should depend on whether the patient has a high likelihood of developing DBF. Our study suggests that patients who present with multiple brain lesions may be more likely to benefit from the addition of WBRT because they appear to be more than twice as likely to develop DBF as compared to patients with a single lesion.
Gamma knife radiosurgery (GKS) has become a well-established treatment modality in the management of selected patients with brain metastasis. The authors review the management of patients with these tumors treated at a single center.

METHODS:
Between 1994 and 2002, 458 consecutive patients with metastatic brain disease underwent GKS. There were 1305 lesions treated in 680 separate sessions. The histological diagnosis was melanoma in 231 (50%), lung cancer in 94 (20.5%), breast cancer in 38 (8.3%), renal cell carcinoma (RCC) in 29 (6.3%), colon carcinoma in 13 (2.8%), unknown primary site in 14 (3.1%), and other in 39 patients (8.5%). The median tumor volume was 0.9 cm³ and the median volume treated was 2.3 cm³. The median radiation dose was 18 Gy prescribed to a median isodose of 60%; the median dose was 20 Gy in melanoma, sarcoma, and RCC. Whole-brain radiotherapy (WBRT) either prior to or following GKS was performed in 114 patients (25%). Follow up ranged from 3 to 84 months with a median of 9 months. The median survival for all patients was 9 months and depended on tumor histology. Survival ranged from 6 months for patients with colon carcinoma, unknown primary tumors, and other tumors to 17 months for those with breast cancer. Median survival in patients with melanoma was 8 months. In multivariate analysis Karnofsky Performance Scale score (< 70 vs > 70), status of systemic disease (yes vs no), histological diagnosis, and total intracranial tumor volume were the only significant factors influencing survival. The number of brain metastases (one-five), WBRT (yes vs no), and age were not significant. Pattern of failure was different in patients with melanoma compared with those with other diagnoses. Cause of death in patients with melanoma was in 50% of the cases due to systemic disease and in 42% due to central nervous system causes, whereas it was 70% for the former and 23% for the latter in patients with other diagnoses. The treatment was well tolerated with significant late toxicity requiring craniotomy for removal of a necrotic focus in only 20 patients (4.7%).

CONCLUSIONS:
Gamma knife radiosurgery provided an excellent palliation with low incidence of toxicity. A Phase III prospective randomized trial is required to define the role of WBRT in combination with GKS.
Application of recursive partitioning analysis and evaluation of the use of whole brain radiation among patients treated with stereotactic radiosurgery for newly diagnosed brain metastases.

Chidel MA, Suh JH, Reddy CA, Chao ST, Lundbeck MF, Barnett GH.

Source
Departments of Radiation Oncology, Cleveland Clinic Foundation, Cleveland, OH 44195, USA.

Abstract
PURPOSE:
To evaluate the usefulness of whole brain radiotherapy (WBRT) and of the Radiation Therapy Oncology Group recursive partitioning analysis (RPA) for brain metastases among patients receiving stereotactic radiosurgery (SRS).

METHODS AND MATERIALS:
A retrospective analysis was performed on 135 patients who underwent linear accelerator (Linac) (n = 73) or Gamma Knife (n = 62) SRS for newly diagnosed brain metastases at the Cleveland Clinic Foundation between 8/89 and 12/98. Univariate and multivariate analyses were performed to evaluate the effects of age, primary site, control of the primary, interval to development of brain metastases (disease-free interval [DFI]), number of brain metastases, presence of extracranial metastases, Karnofsky performance status (KPS), treatment of brain metastases, and RPA class on overall survival.

RESULTS:
Application of the RPA classification revealed 29 patients fit the criteria for class I, 96 for class II, and 10 for class III. All of the patients underwent SRS. Fifty-seven patients also received WBRT at the time of initial presentation (SRS and immediate WBRT), and 78 patients received WBRT only if CNS relapse occurred (SRS alone). The median survival for all patients was 7.9 months (range: 1.1-90.1), and was 11.2 months for RPA class I compared to 6.9 months for RPA classes II-III (p = 0.016). Median survival was 10.5 months following SRS alone compared to 6.4 months following SRS and WBRT (p = 0.07). On univariate analysis, KPS >/= 80% (p = 0.002) and absence of systemic disease (p = 0.013) were also associated with longer survival, whereas control of the primary, DFI, and number of brain metastases did not have an impact. Multivariate analysis revealed only RPA class (p = 0.023) to be an independent predictor for overall survival, whereas treatment group (p = 0.079) was only marginally significant. At 2 years, immediate WBRT improved control at the original site of metastases (80% vs. 52%, p = 0.03) and prevention of new metastatic sites within the brain, 74% vs. 48% (p = 0.06). The 2-year intracranial disease-free survival was 60% following SRS and WBRT compared to only 34% following SRS alone (p = 0.03).

CONCLUSIONS:
Despite the inherent biases to select more favorable patients for SRS, the RPA class retains its prognostic value. Omission of WBRT from the initial management was not detrimental in terms of overall survival; however, progressive disease occurred in over 50% of patients treated in this manner. Further studies are required to determine which, if any, patients should be considered for SRS with WBRT held in reserve.

Stereotactic radiosurgery in the treatment of metastatic disease to the brain.

Source
Department of Neurological Surgery, Keck School of Medicine of the University of Southern California, Los Angeles, USA. josephcc@hsc.usc.edu

Abstract
OBJECTIVE:
In recent years, stereotactic radiosurgery has been growing in popularity as a treatment modality for metastatic disease to the brain. The technique has advantages of reduced cost and low morbidity compared with open surgical treatment. Furthermore, it avoids the potential cognitive side effects of fractionated whole-brain radiotherapy. We undertook this study to determine the usefulness of adjuvant radiation therapy and to determine prognostic factors in patients treated with stereotactic radiosurgery.

METHODS:
We reviewed our series of patients with metastatic tumors treated using gamma knife stereotactic radiosurgery from August 1994 to February 1999. Nonparametric methods were used to compare treatment subgroups by demographic features including age, Karnofsky Performance Scale score, diagnosis, and systemic disease status. Univariate and multivariate analyses of survival and freedom from progression were performed using Kaplan-Meier and Cox proportional hazards regression techniques.

RESULTS:
This study included 190 patients harboring 431 lesions who were treated in 263 treatment sessions. The median follow-up after radiosurgery was 36 weeks for all patients. The median actuarial survival from the time of radiosurgery in all patients was 34 weeks. When patients were stratified according to tumor histology, those without melanoma had a median survival of 39 weeks, and those with melanoma had a median survival of 28 weeks. The cause of death could be determined in 122 (92%) of the patients known to have died during the data capture period. For patients harboring melanoma, death was attributable to systemic disease in 31 (47%), to central nervous system-related processes in 29 (44%), and to unknown causes in 6 (9%). For non-melanoma patients, death was attributable to systemic
disease in 45 (68%), to central nervous system-related processes in 17 (26%), and to unknown causes in 4 (6%). Significantly improved survival (P = 0.002) was observed in patients with controlled systemic disease. No significant difference in survival could be ascertained for patients presenting with up to four lesions, although patients with a total tumor volume greater than 9 cc had shortened survival. No survival benefit could be demonstrated for whole-brain radiotherapy administered either concomitantly or after radiosurgery.

**CONCLUSION:**
Factors correlated with significantly improved survival included controlled systemic disease and non-melanoma histology. We found no significant survival benefit that could be discerned from adjuvant whole-brain radiotherapy in this patient group.

**J Neurosurg. 2005 Jan;102 Suppl:147-50.**
Gamma knife surgery for brain metastases in patients harboring four or more lesions: survival and prognostic factors.
Nam TK, Lee JI, Jung YJ, Im YS, An HY, Nam DH, Park K, Kim JH.

**Source**
Department of Neurosurgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea.

**Abstract**
**OBJECT:**
This study was performed to evaluate the role of gamma knife surgery (GKS) in patients with a large number (four or more) of metastatic brain lesions.

**METHODS:**
The authors retrospectively reviewed the outcome in 130 patients who underwent GKS for metastatic lesions. Eighty-four patients presented with one to three lesions (Group A) and 46 presented with four or more lesions (Group B). The overall median survival time after GKS was 35 weeks. The median survival time in Group A (48 weeks) was significantly longer (p = 0.005) than the survival time in Group B (26 weeks). The recursive partitioning analysis (RPA) class was the only significant prognostic factor identified in multivariate analysis. The median survival for patients in RPA Classes I, II, and III was 72, 48, and 19 weeks, respectively, in Group A and 36 and 13 weeks for Classes II and III in Group B. The number of lesions, tumor volume, whole brain radiotherapy, primary tumor site, age, and sex did not affect survival significantly.

**CONCLUSIONS:**
It is suggested that GKS provides an increase in survival time even in patients with a large number (four or more) of metastatic lesions. Concerning the selection of patients for GKS, RPA class should be
considered as the most important factor and multiplicity of the lesions alone should not be a reason for withholding GKS.

**Technol Cancer Res Treat. 2007 Jun;6(3):153-60.**
Recursive partitioning analysis of prognostic factors for patients with four or more intracranial metastases treated with radiosurgery.
Bhatnagar AK, Kondziolka D, Lunsford LD, Flickinger JC.

**Source**
Departments of Radiation Oncology, Neurological Surgery, Center for Image-Guided Neurosurgery, University of Pittsburgh, School of Medicine, Pittsburgh, PA, USA.

**Abstract**
The purpose of this study was to devise a new recursive partitioning analysis (RPA) of patients with four or more intracranial metastases treated with a single radiosurgery procedure to identify a class of patients with extended survival. 205 patients underwent Gamma Knife radiosurgery for four or more intracranial metastases (median = 5, range 4-18) during one session. The median total treatment volume was 6.8 cc (range 0.6-51.0 cc). Radiosurgery was used as sole management (17% of patients), or in combination with WB-RT (46%), or after failure of WB-RT (38%). The median marginal radiosurgery dose was 16 Gy (range 12-20 Gy). RPA assessed the effects of age, Karnofsky >70, extracranial disease, visceral metastases, number of metastases, total treatment volume, history of breast and melanoma primaries on survival. The median overall survival after radiosurgery for all patients was 8 months. RPA identified a favorable subgroup of 78 patients (43% of the series) with a total treatment volume <7 cc and < 7 brain metastases (Class 1), with a median survival of 13 months. This subgroup's survival was significantly better (p <0.00005) than the remaining patients (Class 2) (n=111) with a median survival of 6 months. In conclusion, RPA of multiple brain metastasis patients identified 2 distinct cohorts of patients. Class 1 patients have a total treatment volume <7 cc and < 7 metastases (4-6) with favorable survival after Radiosurgery and Class 2 patients have a total treatment volume > or = 7 cc and/or > or = 7 metastases and have a significantly poorer survival.

Gamma knife surgery for brain metastases: indications for and limitations of a local treatment protocol.
Serizawa T, Saeki N, Higuchi Y, Ono J, Iuchi T, Nagano O, Yamaura A.

**Source**
Department of Neurosurgery, Chiba Cardiovascular Center, Ichihara, Japan. QWT03231@nifty.ne.jp

**Abstract**
**OBJECTIVE:**
The purpose of this retrospective study was to evaluate results of a local treatment protocol using gamma knife surgery (GKS) for brain metastases without upfront whole brain radiation therapy (WBRT).

METHODS:
Results for 521 consecutive patients satisfying the following 3 criteria were analysed: 1) a maximum of 3 tumours with a diameter of 25 mm or more; 2) no prior WBRT; 3) no surgically in accessible large (>30 mm) tumours. Large tumours were surgically removed and all smaller lesions were treated by GKS without up front WBRT. New lesions, detected with follow-up MRI, were appropriately treated with repeat GKS. Overall survival (OS), neurological survival (NS), qualitative survival (QS) and new lesion-free survival (NLFS) curves were calculated and the prognostic values of covariates were obtained. OS and NS were compared according to tumour number.

RESULTS:
In total, 1023 separate sessions were required to treat 4562 lesions. The primary organs were lung in 369 patients, gastro-intestinal tract in 70, breast in 33, urinary tract in 24, and others/unknown in 25. The median OS period was 9.0 months. On multivariate analysis, the significant prognostic factors for OS were found to be extracranial disease (risk factor: active), Karnofsky performance status (KPS) score (<70) and gender (male). NS and QS at one year were 85.6% and 73.0%, respectively. The only significantly poor prognostic factor for NS was carcinomatous meningitis. NLFS at 6 months was 68.9%. For both OS and NS, the differences between a few (<3) and many (4-10) brain lesions were not significant (OS: p=0.3128, NS: p=0.5509). Patients with numerous (>10) tumours had a significantly poorer prognosis than those with <10.

CONCLUSION:
Our protocol, aggressively applying GKS, provides excellent results in selected patients with <10 brain lesions and no carcinomatous meningitis.

Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial.

Source
Department of Neurosurgery, Thomas Jefferson University Hospital, Philadelphia, PA 19107, USA.
david.andrews@jefferson.edu

Abstract
BACKGROUND:
Brain metastases occur in up to 40% of all patients with systemic cancer. We aimed to assess whether stereotactic radiosurgery provided any therapeutic benefit in a randomised multi-institutional trial directed by the Radiation Therapy Oncology Group (RTOG).

**METHODS:**
Patients with one to three newly diagnosed brain metastases were randomly allocated either whole brain radiation therapy (WBRT) or WBRT followed by stereotactic radiosurgery boost. Patients were stratified by number of metastases and status of extracranial disease. Primary outcome was survival; secondary outcomes were tumour response and local rates, overall intracranial recurrence rates, cause of death, and performance measurements.

**FINDINGS:**
From January, 1996, to June, 2001, we enrolled 333 patients from 55 participating RTOG institutions--167 were assigned WBRT and stereotactic radiosurgery and 164 were allocated WBRT alone. Univariate analysis showed that there was a survival advantage in the WBRT and stereotactic radiosurgery group for patients with a single brain metastasis (median survival time 6.5 vs 4.9 months, p=0.0393). Patients in the stereotactic surgery group were more likely to have a stable or improved Karnofsky Performance Status (KPS) score at 6 months' follow-up than were patients allocated WBRT alone (43% vs 27%, respectively; p=0.03). By multivariate analysis, survival improved in patients with an RPA class 1 (p<0.0001) or a favourable histological status (p=0.0121).

**INTERPRETATION:**
WBRT and stereotactic boost treatment improved functional autonomy (KPS) for all patients and survival for patients with a single unresectable brain metastasis. WBRT and stereotactic radiosurgery should, therefore, be standard treatment for patients with a single unresectable brain metastasis and considered for patients with two or three brain metastases.
prospective randomized clinical trial comparing GK alone, WBRT alone or both. Treatment randomization was stratified by primary tumor site.

METHODS:
Of the 109 patients enrolled in the study, 96 received protocol recommended therapy and are evaluable. Treatment randomization was GK alone: 36, GK + WBRT: 37 and WBRT: 31 patients. Primary sites included non-small cell lung cancer (NSCLC): 62, breast cancer: 12, colorectal cancer: 4, unknown: 7 and miscellaneous: 11 patients. Eligibility criteria included patients with 23 lesions, tumor volume 530 ccs and minimum life expectancy of three months were included. The treatment dose was: GK 30 Gy to the tumor margin. WBRT 30 Gy + GK 20 Gy to the margin, and WBRT 30 Gy in 10 fractions for GK, GK + WBRT and WBRT arms respectively. Fifty-one patients underwent surgical resection of large, symptomatic lesions prior to randomization. All patients had pre and post treatment neurological exam and MRI at GK treatment and at 6 weeks, 3, 6 and 12 month follow-up.

RESULTS:
The overall median survival was 7, 5 and 9 months for the GK, GK + WBRT and WBRT arms respectively. The local control was 87%, 91%. and 62% for GK, GK + WBRT and WBRT alone arms respectively, suggesting that the two radiosurgery arms were superior. However, the occurrence of new brain lesions was lower (43%, 19% and 23% for GK, GK + WBRT and WBRT alone respectively) in the two arms receiving WBRT. Regardless of treatment group, the local control and survival for patients who had surgical resection of brain metastases was 88% and 9 months compared to 73% and 6 months for those without resection suggesting some benefit of surgery. This survival benefit for surgery was not seen in patients who received GK as part of their treatment. Survival of patients by primary site was 6, 9.5 and 7 months for NSCLC, breast and colorectal cancers respectively. Patients with resected primary tumors had a median survival of 9 months compared with 5.5 months for those whose primary tumors were treated with radiation i- chemotherapy respectively.

CONCLUSIONS:
Local control of treated metastatic lesions is superior with the radiosurgery arms. However, the risk of developing new brain lesions is higher for patients not receiving whole brain radiotherapy. There was no difference in overall survival between the three arms. Resection of metastatic lesions did add to overall survival, but not for those receiving radiosurgery. Patients with breast and colorectal cancer fared better than those with lung cancer. Survival was better for patients with resected primary tumors compared to those treated with radiation i- chemotherapy.
Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases.

Kondziolka D, Patel A, Lunsford LD, Kassam A, Flickinger JC.

**Source**
Department of Neurological Surgery, Center for Image-Guided Neurosurgery, University of Pittsburgh, PA, USA.

**Abstract**

**PURPOSE:**
Multiple brain metastases are a common health problem, frequently diagnosed in patients with cancer. The prognosis, even after treatment with whole brain radiation therapy (WBRT), is poor with average expected survivals less than 6 months. Retrospective series of stereotactic radiosurgery have shown local control and survival benefits in case series of patients with solitary brain metastases. We hypothesized that radiosurgery plus WBRT would provide improved local brain tumor control over WBRT alone in patients with two to four brain metastases.

**METHODS:**
Patients with two to four brain metastases (all < or =25 mm diameter and known primary tumor type) were randomized to initial brain tumor management with WBRT alone (30 Gy in 12 fractions) or WBRT plus radiosurgery. Extent of extracranial cancer, tumor diameters on MRI scan, and functional status were recorded before and after initial care.

**RESULTS:**
The study was stopped at an interim evaluation at 60% accrual. Twenty-seven patients were randomized (14 to WBRT alone and 13 to WBRT plus radiosurgery). The groups were well matched to age, sex, tumor type, number of tumors, and extent of extracranial disease. The rate of local failure at 1 year was 100% after WBRT alone but only 8% in patients who had boost radiosurgery. The median time to local failure was 6 months after WBRT alone (95% confidence interval [CI], 3.5-8.5) in comparison to 36 months (95% CI, 15.6-57) after WBRT plus radiosurgery (p = 0.0005). The median time to any brain failure was improved in the radiosurgery group (p = 0.002). Tumor control did not depend on histology (p = 0.85), number of initial brain metastases (p = 0.25), or extent of extracranial disease (p = 0.26). Patients who received WBRT alone lived a median of 7.5 months, while those who received WBRT plus radiosurgery lived 11 months (p = 0.22). Survival did not depend on histology or number of tumors, but was related to extent of extracranial disease (p = 0.02). There was no neurologic or systemic morbidity related to stereotactic radiosurgery.

**CONCLUSIONS:**
Combined WBRT and radiosurgery for patients with two to four brain metastases significantly improves control of brain disease. WBRT alone does not provide lasting and effective care for most patients.

3. Meningiomas

Meningiomas are considered a classical indication for open microsurgery, but the surgical resection has to be complete to avoid local tumour recurrences. Microsurgery has developed considerably within the recent decade but reaches its natural limitations in many anatomical locations in the brain. In many situations a complete resection of a meningiomas is still difficult to achieve without significant side effects.

Gamma Knife radiosurgery has gained an important role to complete microsurgery in order to achieve long-term tumour control. Gamma Knife treatment allows a less aggressive surgical approach with lower morbidity and less complications. The aim of Gamma Knife treatments of meningioma is to achieve a growth arrest, the so called local tumour control.

This local tumor control was achieved in 88.9-98% in eleven published Gamma Knife studies comprising 2108 meningioma patients. The recently published European Multicenter Gamma Knife Study of 3768 patients demonstrated a 5-year tumour control in 95% of patients who had been treated in the Gamma Knife (Santacroce 2011).

The Gamma Knife treatment however, has a clear limitation in the tumor volume. In larger tumours the neurosurgical tumour removal is essential, but the more “sensitible” parts of the tumor can be left in place and later be treated with the Gamma knife. The natural consequence is a reduced need for surgical aggressiveness and morbidity.

In summary Gamma Knife radiosurgery allows less aggressive or minimal invasive tumour resections and helps to reduce treatment induced side effects.

Selected Literature 1999-2012 : Gamma Knife Radiosurgery for Meningioma

**VERY IMPORTANT**

**Neurosurgery. 2012 Jan;70(1):32-9; discussion 39.**

Long-term tumor control of benign intracranial meningiomas after radiosurgery in a series of 4565 patients.

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

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

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

RESULTS:
Median tumor volume was 4.8 cm³, and median dose to tumor margin was 14 Gy. All tumors with imaging follow-up < 24 months were excluded. Detailed results from 3768 meningiomas (71%) were analyzed. Median imaging follow-up was 63 months. The volume of treated tumors decreased in 2187 lesions (58%), remained unchanged in 1300 lesions (34.5%), and increased in 281 lesions (7.5%), giving a control rate of 92.5%. Only 84 (2.2%) enlarging tumors required further treatment. Five- and 10-year progression-free survival rates were 95.2% and 88.6%, respectively. Tumor control was higher for imaging defined tumors vs grade I meningiomas (P < .001), for female vs male patients (P < .001), for sporadic vs multiple meningiomas (P < .001), and for skull base vs convexity tumors (P < .001). Permanent morbidity rate was 6.6% at the last follow-up.

CONCLUSION:
Radiosurgery is a safe and effective method for treating benign meningiomas even in the medium to long term.
PURPOSE:
To define the rate of tumor control and factors associated with radiation-related complications after single-fraction radiosurgery (SRS) for patients with imaging defined intracranial meningiomas.

MATERIALS AND METHODS:
Retrospective review of 251 patients (192 women, 59 men) having SRS for imaging-defined intracranial meningiomas between 1990 and 2008. Excluded were patients with radiation-induced tumors, meningiomatosis, or neurofibromatosis. The mean patient age was 58.6 ± 13.4 years. The majority of tumors involved the skull base/tentorium (n = 210, 83.7%). The mean treatment volume was 7.7 ± 6.2 cm(3); the mean tumor margin dose was 15.8 ± 2.0 Gy. Follow-up (mean, 62.9 ± 43.9 months) was censored at last evaluation (n = 224), death (n = 22), or tumor resection (n = 5).

RESULTS:
No patient died from tumor progression or radiation-related complications. Tumor size decreased in 181 patients (72.1%) and was unchanged in 67 patients (26.7%). Three patients (1.2%) had in-field tumor progression noted at 28, 145, and 150 months, respectively. No patient had a marginal tumor progression. The 3- and 10-year local control rate was 99.4%. One patient had distant tumor progression at 105 months and underwent repeat SRS. Thirty-one patients (12.4%) had either temporary (n = 8, 3.2%) or permanent (n = 23, 9.2%) symptomatic radiation-related complications including cranial nerve deficits (n = 14), headaches (n = 5), hemiparesis (n = 5), new/worsened seizure (n = 4), cyst-formation (n = 1), hemifacial spasm (n = 1), and stroke (n = 1). The 1- and 5-year complication rates were 8.3% and 11.5%, respectively. Radiation-related complications were associated with convexity/falx tumors (HR = 2.8, 95% CI 1.3-6.1, p = 0.009) and increasing tumor volume (HR = 1.05, 95% CI 1.0-1.1, p = 0.04) on multivariate analysis. No patient developed a radiation-induced tumor.

CONCLUSIONS:
Single-fraction SRS at the used dose range provides a high rate of tumor control for patients with imaging defined intracranial meningiomas. However, treatment failures were noted after 10 years emphasizing the need for long-term imaging follow-up after meningioma SRS.
OBJECT:
Skull base meningiomas are challenging tumors owing in part to their close proximity to important neurovascular structures. Complete microsurgical resection can be associated with significant morbidity, and recurrence rates are not inconsequential. In this study, the authors evaluate the outcomes of skull base meningiomas treated with Gamma Knife surgery (GKS) both as an adjunct to microsurgery and as a primary treatment modality.

METHODS:
The authors performed a retrospective review of a prospectively compiled database detailing the outcomes in 255 patients with skull base meningiomas treated at the University of Virginia from 1989 to 2006. All patients had a minimum follow-up of 24 months. The group comprised 54 male and 201 female patients, with a median age of 55 years (range 19-85 years). One hundred nine patients were treated with upfront radiosurgery, and 146 patients were treated with GKS following resection. Patients were assessed clinically and radiographically at routine intervals following GKS. Factors predictive of new neurological deficit following GKS were assessed via univariate and multivariate analysis, and Kaplan-Meier analysis and Cox multivariate regression analysis were used to assess factors predictive of tumor progression.

RESULTS:
Meningiomas were centered over the cerebellopontine angle in 43 patients (17%), the clivus in 40 (16%), the petroclival region in 28 (11%), the petrous region in 6 (2%), and the parasellar region in 138 (54%). The median duration of follow-up was 6.5 years (range 2-18 years). The mean preradiosurgery tumor volume was 5.0 cm$^3$ (range 0.3-54.8 cm$^3$). At most recent follow-up, 220 patients (86%) displayed either no change or a decrease in tumor volume, and 35 (14%) displayed an increase in volume. Actuarial progression-free survival at 3, 5, and 10 years was 99%, 96%, and 79%, respectively. In Cox multivariate analysis, pre-GKS covariates associated with tumor progression included age greater than 65 years (HR 3.41, 95% CI 1.63-7.13, p = 0.001) and decreasing dose to tumor margin (HR 0.90, 95% CI 0.80-1.00, p = 0.05). At most recent clinical follow-up, 230 patients (90%) demonstrated no change or improvement in their neurological condition and the condition of 25 patients had deteriorated (10%). In multivariate analysis, the factors predictive of new or worsening symptoms were increasing duration of follow-up (OR 1.01, 95% CI 1.00-1.02, p = 0.015), tumor progression (OR 2.91, 95% CI 1.60-5.31, p < 0.001), decreasing maximum dose (OR 0.90, 95% CI 0.84-0.97, p = 0.003), and increasing pretreatment tumor volume (OR 1.03, 95% CI 1.01-1.04, p = 0.007).
CI 0.84-0.97, \( p = 0.007 \), and petrous or clival location versus parasellar, petroclival, and cerebellopontine angle location (OR 3.47, 95% CI 1.23-9.74, \( p = 0.018 \)).

**CONCLUSIONS:**
Stereotactic radiosurgery offers a high rate of tumor control and neurological preservation in patients with skull base meningiomas. After radiosurgery, better outcomes were observed for those receiving an optimal radiosurgery dose and harboring tumors located in a cerebellopontine angle, parasellar, or petroclival location.

Gamma Knife surgery for parasellar meningiomas: long-term results including complications, predictive factors, and progression-free survival.

Department of Neurological Surgery, University of Virginia Health System, Charlottesville, Virginia 22908, USA.

**OBJECT:**
Stereotactic radiosurgery serves as an important primary and adjuvant treatment option for patients with many types of intracranial meningiomas. This is particularly true for patients with parasellar meningiomas. In this study, the authors evaluated the outcomes of Gamma Knife surgery (GKS) used to treat parasellar meningiomas.

**METHODS:**
The study is a retrospective review of the outcomes in 138 patients with meningiomas treated at the University of Virginia from 1989 to 2006; all patients had a minimum follow-up of 24 months. There were 31 men and 107 women whose mean age was 54 years (range 19-85 years). Eighty-four patients had previously undergone resection. The mean pre-GKS tumor volume was 7.5 ml (range 0.2-54.8 ml). Clinical and radiographic evaluations were performed, and factors related to favorable outcomes in each case were assessed.

**RESULTS:**
The mean follow-up duration was 84 months (median 75.5 months, range 24-216 months). In 118 patients (86%), the tumor volume was unchanged or had decreased at last follow-up. **Kaplan-Meier analysis demonstrated radiographic progression-free survival at 5 and 10 years to be 95.4% and 69%,** respectively. Fourteen patients (10%) developed new cranial nerve palsies following GKS. Factors associated with tumor control included younger age, a higher isodose, and smaller tumor volume. A longer follow-up duration was associated with either a decrease or increase in tumor volume. Fourteen patients (10%) experienced new or worsening cranial nerve deficits after treatment. Factors
associated with this occurrence were larger pretreatment tumor volume, lower peripheral radiation dose, lower maximum dose, tumor progression, and longer follow-up.

CONCLUSIONS:
Gamma Knife surgery offers an acceptable rate of tumor control for parasellar meningiomas and accomplishes this with a low incidence of neurological deficits. Radiological control after radiosurgery is more likely in those patients with a smaller tumor volume and a higher prescription dose.

Gamma Knife surgery for convexity, parasagittal, and falcine meningiomas.
Hasegawa T, Kida Y, Yoshimoto M, Iizuka H, Ishii D, Yoshida K.

Department of Neurosurgery, Gamma Knife Center, Komaki City Hospital, Komaki, Aichi, Japan. h-toshi@komakihp.gr.jp

OBJECT:
The aim of this study was to evaluate the outcomes in patients with convexity, parasagittal, or falcine meningiomas treated using Gamma Knife surgery (GKS) and to determine management strategy considering a risk of radiation-induced edema.

METHODS:
One hundred twelve patients who harbored 125 convexity, parasagittal, or falcine meningiomas were assessed. Forty-six patients underwent GKS as the initial treatment. The median tumor diameter was 25 mm, and median tumor volume was 8 cm(3). The median maximum and margin doses were 30 and 16 Gy, respectively.

RESULTS:
The median follow-up period was 72 months. The actuarial 5- and 10-year progression-free survival rates were 78% and 55%, respectively. The actuarial 5- and 10-year local tumor control rates were 87% and 71%, respectively. Of 29 tumors that developed postradiosurgical edema, 7 were symptomatic. The actuarial symptomatic radiation-induced edema rate was 7%. The incidence of this complication was significantly higher in patients who underwent GKS as the initial treatment. Six of 46 patients for whom GKS was the initial treatment had preradiosurgical edema. Of these 6 patients, 4 developed severe panhemispheric edema after GKS (2 patients with parasagittal tumors, 1 with a falx tumor, and 1 with a convexity tumor).

CONCLUSIONS:
Gamma Knife surgery is an effective treatment for convexity, parasagittal, and falcine meningiomas as the initial or adjuvant treatment. However, GKS should be restricted to small- to medium-sized tumors,
particularly in patients with primary tumors, because radiation-induced edema is more common in convexity, parasagittal, and falcine meningiomas than skull base meningiomas.

Stereotactic radiosurgery for WHO grade I meningiomas.
Sheehan JP, Williams BJ, Yen CP.

Department of Neurological Surgery, University of Virginia Health Sciences Center, Charlottesville, Virginia 22908, USA. jps2f@virginia.edu

Meningiomas represent a common intracranial tumor in the adult population. Although extirpation to achieve a gross total resection or at least decrease mass effect has been the mainstay of treatment, stereotactic radiosurgery has come to play an increasingly important role in the management of patients with meningiomas. Radiosurgery utilizes highly focused, beams of ionizing radiation to inactivate tumor cells. Image guidance and a steep dose fall off are critical features of this approach. The radiobiology of radiosurgery differs in certain advantageous ways from conventional radiotherapy. Radiosurgery initially was utilized to treat recurrent or residual skull base meningiomas. As success was observed in this setting, radiosurgery has gradually expanded its role so as to treat convexity meningiomas; it is also used as an upfront treatment for patients for whom clinical and neuro-imaging findings are consistent with a meningioma. Most large series demonstrate tumor control rates for patients with grade I meningiomas in excess of 85%. Neurological function is generally preserved or improved for patients with meningiomas. However, complications can occur. Longitudinal follow-up including neurologic and radiologic assessment is required. Single and multisession stereotactic radiosurgery will likely play an expanded role in the treatment of patients with meningiomas.

Long-term outcomes and patterns of tumor progression after gamma knife radiosurgery for benign meningiomas.

Department of Neurosurgery, Keck School of Medicine, University of Southern California, Los Angeles, California, USA. gzada@usc.edu

OBJECT:
To characterize the timing and patterns of long-term treatment failure after Gamma Knife radiosurgery (GKRS) for benign meningiomas.
METHODS:
Data were retrospectively reviewed in 116 patients who underwent 136 GKRS treatments for benign intracranial meningiomas from 1996 to 2004. Patients with atypical or malignant meningiomas were excluded. Surgical resection preceded GKRS in 72 patients (62%). The median tumor volume was 3.4 cm, and the median prescription dose to the 50% isodose line was 16 Gy.

RESULTS:
The median follow-up time was 75 months (range, 4-146 months). Overall tumor control was achieved in 128 of 136 lesions (94%), of which tumor size was stable in 68% and decreased in 26%. Seven patients experienced disease progression in 8 tumors, occurring at a mean time of 90 months. The overall 5-year and 10-year actuarial tumor control rate was 98.9% and 84%, respectively. Characteristics corresponding to tumor progression included insufficient tumor coverage (98% vs 93%, P = .007), cavernous sinus lesions, and meningiomatosis. Complications after GKRS developed in 8% of patients, in whom the mean tumor volume was nearly double that in patients with no adverse effects (11 vs 5.7 cm3, P = .003).

CONCLUSIONS:
GKRS demonstrates excellent long-term tumor control in the management of benign meningiomas. Tumor progression occurred at a mean time of 7.5 years after GKRS, reinforcing the need for long-term surveillance despite initial tumor control. Treatment failure was related to undercoverage of lesions in the majority of cases, with the remainder demonstrating evidence of abnormal tumor biology.

Gamma knife surgery of meningiomas involving the cavernous sinus: long-term follow-up of 100 patients.
Skeie BS, Enger PO, Skeie GO, Thorsen F, Pedersen PH.
Department of Neurosurgery, Haukeland University Hospital, N-5021 Bergen, Norway. bsai@helse-bergen.no

OBJECTIVE:
Resection of meningiomas involving the cavernous sinus often is incomplete and associated with considerable morbidity. As a result, an increasing number of patients with such tumors have been treated with gamma knife surgery (GKS). However, few studies have investigated the long-term outcome for this group of patients.

METHODS:
100 patients (23 male/77 female) with meningiomas involving the cavernous sinus received GKS at the Department of Neurosurgery at Haukeland University Hospital, Bergen, Norway, between November 1988 and July 2006. They were followed for a mean of 82.0 (range, 0-243) months. Only 2 patients were lost to long-term follow-up. Sixty patients underwent craniotomy before radiosurgery, whereas radiosurgery was the primary treatment for 40 patients.

RESULTS:
Tumor growth control was achieved in 84.0% of patients. Twelve patients required re-treatment: craniotomy (7), radiosurgery (1), or both (4). Three out of 5 patients with repeated radiosurgery demonstrated secondary tumor growth control. Excluding atypical meningiomas, the growth control rate was 90.4%. The 1-, 5-, and 10-year actuarial tumor growth control rates are 98.9%, 94.2%, and 91.6%, respectively. Treatment failure was preceded by clinical symptoms in 14 of 15 patients. Most tumor growths appeared within 2.5 years. Only one third grew later (range, 6-20 yr). The complication rate was 6.0%: optic neuropathy (2), pituitary dysfunction (3), worsening of diplopia (1), and radiation edema (1). Mortality was 0. At last follow-up, 88.0% were able to live independent lives.

CONCLUSION:
GKS gives long-term growth control and has a low complication rate. Most tumor growths manifest within 3 years following treatment. However, some appear late, emphasizing the need for long-term follow-up.

Stereotactic radiosurgery for skull base meningioma.
Igaki H, Maruyama K, Koga T, Murakami N, Tago M, Terahara A, Shin M, Nakagawa K, Ohtomo K.
Department of Radiology, Teikyo University School of Medicine, Tokyo, Japan. ki-ty@umin.ac.jp

Stereotactic radiosurgery is now a treatment option for meningiomas, especially for high-risk patients such as those with skull base lesions. The clinical outcomes were retrospectively analyzed of stereotactic radiosurgery using the Leksell Gamma Knife® performed for 98 patients with 106 skull base meningiomas at the University of Tokyo Hospital between June 1990 and April 2006 and followed up for more than a year. After a median follow-up period of 53.2 months (range 12.2-204.4 months), local tumor control rates were 86.9% and 78.9% at 5 years and 10 years, respectively. Tumors with volume of 4 cm(3) or smaller (97.5% vs. 76.1% at 5 years, p = 0.001) and tumors completely included within the isodose line of 14 Gy or more (97.5% vs. 67.2% at 5 years, p = 0.0006) had higher local control rates. Postoperative residual tumors treated by stereotactic radiosurgery were controlled in all 25 cases. Cranial nerve deficits were improved, stable, and deteriorated in 12, 64, and 3 patients, respectively, after stereotactic radiosurgery. Stereotactic radiosurgery was effective treatment...
method for local control of skull base meningiomas, especially for small or postoperative residual tumors. Correct combination of microsurgery and radiosurgery leads to excellent local control.

**J Neurosurg. 2010 May;112(5):957-64.**


Department of Neurological Surgery, University of Pittsburgh, Pennsylvania 15213, USA.

**OBJECT:**

Because of their critical location adjacent to brain, cranial nerve, and vascular structures, petroclival meningiomas remain a clinical challenge. The authors evaluated outcomes in 168 patients with petroclival meningiomas who underwent Gamma Knife surgery (GKS) during a 21-year interval.

**METHODS:**

Gamma Knife surgery was used as either primary or adjuvant treatment of 168 petroclival meningiomas involving the region between the petrous apex and the upper two-thirds of the clivus. The most common presenting symptoms were trigeminal nerve dysfunction, balance problems, diplopia, and hearing loss. The median tumor volume was 6.1 cm³ (range 0.3-32.5 cm³), and the median radiation dose to the tumor margin was 13 Gy (range 9-18 Gy).

**RESULTS:**

During a median follow-up of 72 months, neurological status improved in 44 patients (26%), remained stable in 98 (58%), and worsened in 26 (15%). Tumor volume decreased in 78 patients (46%), remained stable in 74 (44%), and increased in 16 (10%), all of whom were subjected to additional management strategies. Overall 5- and 10-year progression-free survival rates were 91 and 86%, respectively. Patients followed up for at least 10 years (31 patients) had tumor and symptom control rates of 97 and 94%, respectively. Eight patients had repeat radiosurgery, 4 underwent delayed resection, and 4 had fractionated radiation therapy. Cerebrospinal fluid diversion was performed in 7 patients (4%). Significant risk factors for tumor progression were a tumor volume > or = 8 cm³ (p = 0.001) and male sex (p = 0.02).

**CONCLUSIONS:**

In this 21-year experience, GKS for petroclival meningiomas obviated initial or further resection in 98% of patients and was associated with a low risk of adverse radiation effects. The authors believe that radiosurgery should be considered as an initial option for patients with smaller-volume, symptomatic petroclival meningiomas.
OBJECT:
Meningiomas of the cerebral convexity are often surgically curable because both the mass and involved dura mater can be removed. Stereotactic radiosurgery has become an important primary or adjuvant treatment for patients with intracranial meningiomas. The authors evaluated clinical and imaging outcomes in patients with convexity meningiomas after radiosurgery.

METHODS:
The patient cohort consisted of 125 patients with convexity meningiomas managed using radiosurgery at some point during an 18-year period. The patient series included 76 women, 55 patients who had undergone prior resection, and 6 patients with neurofibromatosis Type 2. Tumors were located in frontal (80 patients), parietal (24 patients), temporal (12 patients), and occipital (9 patients) areas. The WHO tumor grades in patients with prior resections were Grade I in 34 patients, Grade II in 15 patients, and Grade III in 6 patients. Seventy patients underwent primary radiosurgery and therefore had no prior histological tumor diagnosis. The mean tumor volume was 7.6 ml. Radiosurgery was performed using the Leksell Gamma Knife with a mean tumor margin dose of 14.2 Gy.

RESULTS:
Serial imaging was evaluated in 115 patients (92%). After primary radiosurgery, the tumor control rate was 92%. After adjuvant radiosurgery, the control rate was 97% for Grade I tumors. The actuarial tumor control rates at 3 and 5 years for the entire series were 86.1 +/- 3.8% and 71.6 +/- 8.6%, respectively. For patients with benign tumors (Grade I) and those without prior surgery, the actuarial tumor control rate was 95.3 +/- 2.3% and 85.8 +/- 9.3%, respectively. Delayed resection after radiosurgery was performed in 9 patients (7%) at an average of 35 months. No patient developed a subsequent radiation-induced tumor. The overall morbidity rate was 9.6%. Symptomatic peritumoral imaging changes compatible with edema or adverse radiation effects developed in 5%, at a mean of 8 months.

CONCLUSIONS:
Stereotactic radiosurgery provides satisfactory control rates either after resection or as an alternate to resection, particularly for histologically benign meningiomas. Its role is most valuable for patients whose tumors affect critical neurological regions and who are poor candidates for resection. Both temporary and permanent morbidity are related to brain location and tumor volume.

Iwai Y, Yamanaka K, Ikeda H.

Department of Neurosurgery, Osaka City General Hospital, Osaka, Japan. y-iwai@rc5.so-net.ne.jp

OBJECT:
In this study, the authors evaluate the long-term results after Gamma Knife radiosurgery of cranial base meningiomas. This study is a follow-up to their previously published report on the early results.

METHODS:
Between January 1994 and December 2001, the authors treated benign cranial base meningiomas in 108 patients using low-dose Gamma Knife radiosurgery. The tumor volumes ranged from 1.7 to 55.3 cm³ (median 8.1 cm³), and the radiosurgery doses ranged from 8 to 12 Gy (median 12 Gy) to the tumor margin.

RESULTS:
The mean duration of follow-up was 86.1 months (range 20-144 months). Tumor volume decreased in 50 patients (46%), remained stable in 51 patients (47%), and increased (local failure) in 7 patients (6%). Eleven patients experienced tumor recurrence outside the treatment field. Among these patients, marginal failure was seen in 5 and distant recurrence was seen in 6. Seven patients were thought to have malignant transformation based on histological or radiological characteristics of the lesion. The actuarial progression-free survival rate, including malignant transformation and outside recurrence, was 93% at 5 years and 83% at 10 years. Neurological status improved in 16 patients (15%). Permanent radiation injury occurred in 7 patients (6%).

CONCLUSIONS:
Gamma Knife radiosurgery is a safe and effective treatment for cranial base meningiomas as demonstrated with a long-term follow-up period of > 7 years. Surgeons must be aware of the possibility of treatment failure, defined as local failure, marginal failure, and malignant transformation; however, this may be the natural course of meningiomas and not related to radiosurgery.
**Prog Neurol Surg. 2009;22:96-111.**
Gamma knife radiosurgery for skull-base meningiomas.
Takanashi M, Fukuoka S, Hojyo A, Sasaki T, Nakagawara J, Nakamura H.

Department of Neurosurgery, Nakamura Memorial Hospital, Sapporo, Hakkaido, Japan.

**OBJECTIVE:**
The primary purpose of this study was to evaluate the efficacy of gamma knife radiosurgery (GKRS) when used as a treatment modality for cavernous sinus or posterior fossa skull-base meningiomas (SBMs), with particular attention given to whether or not intentional partial resection followed by GKRS constitutes an appropriate combination treatment method for larger SBMs.

**PATIENTS AND METHODS:**
Of the 101 SBM patients in this series, 38 were classified as having cavernous sinus meningiomas (CSMs), and 63 presented with posterior fossa meningiomas (PFMs). The patients with no history of prior surgery (19 CSMs, 57 PFMs) were treated according to a set protocol. Small to medium-sized SBMs were treated by GKRS only. To minimize the risk of functional deficits, larger tumors were treated with the combination of intentional partial resection followed by GKRS. Residual or recurrent tumors in patients who had undergone extirpations prior to GKRS (19 CSMs, 6 PFMs) are not eligible for this treatment method (due to the surgeries not being performed as part of a combination strategy designed to preserve neurological function as the first priority).

**RESULTS:**
The mean follow-up period was 51.9 months (range, 6-144 months). The overall tumor control rates were 95.5% in CSMs and 98.4% in PFMs. Nearly all tumors treated with GKRS alone were well controlled and the patients had no deficits. Furthermore, none of the patients who had undergone prior surgeries experienced new neurological deficits after GKRS. While new neurological deficits appeared far less often in those receiving the combination of partial resection with subsequent GKRS, extirpations tended to be associated with not only a higher incidence of new deficits but also a significant increase in the worsening of already-existing deficits.

**CONCLUSION:**
Our results indicate that GKRS is a safe and effective primary treatment for SBMs with small to moderate tumor volumes. We also found that larger SBMs compressing the optic pathway or brain stem can be effectively treated, minimizing any possible functional damage, by a combination of partial resection with subsequent GKRS.
Gamma knife radiosurgery for skull base meningiomas: long-term radiologic and clinical outcome.

Han JH, Kim DG, Chung HT, Park CK, Paek SH, Kim CY, Jung HW.

Department of Neurosurgery, Seoul National University College of Medicine, Seoul, Korea.

PURPOSE:
To analyze the long-term outcomes in patients with skull base meningiomas (SBMNGs) treated with Gamma Knife radiosurgery (GKRS).

METHODS AND MATERIALS:
Of the 98 consecutive patients with SBMNGs treated with GKRS between 1998 and 2002, 63 were followed up for more than 48 months. The mean (+/-SD) age of the patients was 50 +/- 12 years, the mean tumor volume was 6.5 cm(3) (range, 0.5-18.4 cm(3)), the mean marginal dose was 12.6 Gy (range, 7.0-20.0 Gy), and the mean follow-up duration was 77 +/- 18 months. The mean number of shots was 13.7 +/- 3.8. The tumor volume was decreased at the last follow-up in 28 patients (44.4%) and increased in 6 (9.6%). The actuarial tumor control rate was 90.2% at 5 years. No notable prognostic factor related to tumor control was identified. Ten patients (15.9%) with a cranial neuropathy showed unfavorable outcomes. The rate of improvement in patients with a cranial neuropathy was 45.1%. Age >70 years was likely correlated with an unfavorable outcome in patients with cranial neuropathy (odds ratio = 0.027; p = 0.025; 95% confidence interval 0.001-0.632). Cavernous sinus location was significantly associated with improvement of a cranial neuropathy (odds ratio = 7.314; p = 0.007; 95% confidence interval 1.707-31.34).

CONCLUSIONS:
Gamma Knife radiosurgery is an effective modality for the treatment of SBMNGs and provides favorable outcomes in patients with cranial neuropathy, even in the long-term follow-up period. However, radiosurgery for patients with no or only mild symptoms should be performed cautiously because neither complication rate is low enough to be negligible, especially in elderly patients. A cranial neuropathy by MNGs involving the cavernous sinus seems to have a higher chance of improvement after radiosurgery than other SBMNGs.
Radiosurgery as definitive management of intracranial meningiomas.
Kondziolka D, Mathieu D, Lunsford LD, Martin JJ, Madhok R, Niranjan A, Flickinger JC.

Department of Neurological Surgery, The Center for Image-guided Neurosurgery, University of Pittsburgh, Pittsburgh, Pennsylvania 15213, USA. kondziolkads@upmc.edu

OBJECTIVE:
Stereotactic radiosurgery has become an important primary or adjuvant minimally invasive management strategy for patients with intracranial meningiomas with the goals of long-term tumor growth prevention and maintenance of patient neurological function. We evaluated clinical and imaging outcomes of meningiomas stratified by histological tumor grade.

METHODS:
The patient cohort consisted of 972 patients with 1045 intracranial meningiomas managed during an 18-year period. The series included 70% women, 49% of whom had undergone a previous resection and 5% of whom had received previous fractionated radiation therapy. Tumor locations included middle fossa (n = 351), posterior fossa (n = 307), convexity (n = 126), anterior fossa (n = 88), parasagittal region (n = 113), or other (n = 115).

RESULTS:
The overall control rate for patients with benign meningiomas (World Health Organization Grade I) was 93%. In those without previous histological confirmation (n = 482), tumor control was 97%. However, for patients with World Health Organization Grade II and III tumors, tumor control was 50 and 17%, respectively. Delayed resection after radiosurgery was necessary in 51 patients (5%) at a mean of 35 months. After 10 years, Grade 1 tumors were controlled in 91% (n = 53); in those without histology, 95% (n = 22) were controlled. None of the patients developed a radiation-induced tumor. The overall morbidity rate was 7.7%. Symptomatic peritumoral imaging changes developed in 4% of the patients at a mean of 8 months.

CONCLUSION:
Stereotactic radiosurgery provided high rates of tumor growth control or regression in patients with benign meningiomas with low risk. This study confirms the role of radiosurgery as an effective management choice for patients with small to medium-sized symptomatic, newly diagnosed or recurrent meningiomas of the brain.
Gamma-knife radiosurgery for cranial base meningiomas: experience of tumor control, clinical course, and morbidity in a follow-up of more than 8 years.
Department of Neurosurgery, Medical University of Vienna, Vienna, Austria.

OBJECTIVE:
Surgical resection of cranial base meningiomas is often limited owing to involvement of crucial neural structures. Within the last 2 decades Gamma Knife radiosurgery (GKRS) has gained increasing importance as an adjunct treatment after incomplete resection and as an alternative treatment to open surgery. However, reports of long-term results are still sparse. We therefore performed this study to analyze the long-term results of GKRS treatment of cranial base meningiomas, following our previously published early follow-up experience.

METHODS:
A retrospective analysis of the medical files for Gamma Knife and surgical treatments, clinicoradiological findings, and outcome was carried out focusing on tumor control, clinical course, and morbidity.

RESULTS:
Between 1992 and 1995, we treated 36 patients with cranial base meningiomas using GKRS (male:female ratio, 1:5; mean age, 59 yr; range, 44-89 yr). Twenty-five patients were treated with GKRS after open surgery, and 11 patients received GKRS alone. Tumor control, neurological outcomes, and adverse effects were analyzed after a long-term follow-up period (mean, 103 mo; range, 70-133 mo) and compared with our previous results after an early follow-up period (mean, 48 mo; range, 36-76 mo). Control of tumor growth was achieved in 94% of patients. Compared with the early follow-up period, the late neuroradiological effects of GKRS on cranial base meningiomas were continuing tumor shrinkage in 11 patients (33%), stable tumor size in 20 patients (64%) and tumor progression in two meningiomas (6%). The neurological status improved in 16 patients (44%), remained stable in 19 patients (52%), and deteriorated in one patient (4%). Adverse side effects of GKRS were found only during the early follow-up period.

CONCLUSION:
Our data confirm that GKRS is not only a safe and effective treatment modality for cranial base meningiomas in short-term observation, but also in a mean long-term follow-up period of more than 8 years. Tumor shrinkage and clinical improvement also continued during the longer follow-up period.
Long term experience of gamma knife radiosurgery for benign skull base meningiomas.
Kreil W, Luggin J, Fuchs I, Weigl V, Eustacchio S, Papaefthymiou G.
Department of Neurosurgery, Medical University Graz, Graz, Austria.

OBJECTIVES:
As most reports on the gamma knife have related only to short or mid-term results, we decided to evaluate the effectiveness and toxicity of radiosurgical treatment for benign skull base meningiomas in 200 patients with a follow up of 5-12 years to define the role of gamma knife radiosurgery (GKRS) for basal meningiomas and to provide further data for comparison with other treatment options.

METHODS:
In total, 99 patients were treated with a combination of microsurgical resection and GKRS. In 101 patients, GKRS was performed as the sole treatment option. Tumour volumes ranged from 0.38 to 89.8 cm³ (median 6.5 cm³), and doses of 7-25 Gy (median 12 Gy) were given to the tumour borders at covering isodose volume curves (range 20-80%, median 45%).

RESULTS:
The actuarial progression free survival rate was 98.5% at 5 years and 97.2% at 10 years. Passing radiation induced oedema occurred in two patients (1%). The neurological status improved in 83 cases (41.5%), remained unaltered in 108 (54%), and deteriorated in 9 (4.5%). Worsening was transient in seven patients (3.5%) and unrelated to tumour or treatment in one (0.5%). Repeated microsurgical resection was performed in five patients following GKRS (2.5%).

CONCLUSIONS:
GKRS has proved to be an effective alternative to microsurgical resection, radiotherapy, and Linac based radiosurgery for adjunctive and primary treatment of selected patients with basal meningiomas. Because of the excellent long term tumour control rate and low morbidity associated with GKRS, this treatment option should be used more frequently in the therapeutic management of benign skull base meningiomas.
The use of stereotactic radiosurgery in the management of meningiomas.
Malik I, Rowe JG, Walton L, Radatz MW, Kemeny AA.

National Centre for Stereotactic Radiosurgery, Royal Hallamshire Hospital, Sheffield, UK.

This is a systematic review of a consecutive series of 309 meningiomas treated with gamma knife stereotactic radiosurgery between 1994 and 2000. There was an extreme selection bias towards lesions unfavourable for surgery, determined by the patients referred for treatment: 70% of tumours involved the skull base, 47% specifically the cavernous sinus: 15% of patients had multiple meningiomatosis or type 2 neurofibromatosis. Tumour histology was the main determinant of growth control (p < 0.001), the 5-year actuarial control rates being 87% for typical meningiomas, 49% for atypical tumours and 0% for malignant lesions. Complications from radiosurgery were rare, occurring in 3% of tumours, and were most frequently trigeminal and eye movement disturbances treating cavernous sinus meningiomas. Given the problems inherent in managing these tumours, radiosurgery is a valuable strategy and adjuvant treatment for these meningiomas.

Gamma knife radiosurgery of skull base meningiomas.

Department of Stereotactic and Radiation Neurosurgery, Na Homolce Hospital, Prague, Czech Republic.

Meningiomas are the most frequent benign tumors treated by gamma knife radiosurgery and the majority of them are located on the skull base. Between 1992 and 1999, 197 skull base-located meningiomas in 192 patients were treated by gamma knife in Prague. Contact with the chiasma or optic tract was not regarded as a contraindication for gamma knife radiosurgery and such contact was observed in 32% of the skull base meningiomas treated. 176 patients were monitored during a median of 36 months, of whom 73% showed a decrease in tumor volume; no change was observed in 25% and continued growth was observed in 2%. Neurodeficit improved in 63% of patients, temporary morbidity occurred in 11% and persistent morbidity remained in 4.5%. Radiosurgery induced edema in 11%. Significantly lower edema occurrence was observed after radiosurgery in patients with no history of edema prior to radiosurgery, where the tumor was located in the posterior skull base and where the dosage to the tumor margin was lower than or equal to 14 Gy. Radiosurgery of skull base meningiomas has been proven to be safe and efficient. We consider gamma knife treatment for skull base meningiomas to be the method of choice whenever tumors are within the volume limits and there is no need for an urgent decompressive effect from the open operation.
**Neurosurg Focus. 2003 May 15;14(5):e4.**

Stereotactic radiosurgery for intracranial meningiomas: indications and results.
Pollock BE.

Department of Neurologic Surgery and the Division of Radiation Oncology, Mayo Clinic and Foundation, Rochester, Minnesota 55905, USA.

**OBJECT:**
Stereotactic radiosurgery (SRS) has become an important treatment option for patients with intracranial meningiomas. The author reviews the 12-year experience at a single institution and discusses the relative strengths and weakness of this management approach.

**METHODS:**
Between January 1990 and December 2002, 330 patients (with 356 tumors) underwent radiosurgery for intracranial meningiomas. One hundred thirty-eight patients (42%) harbored recurrent/residual tumors after having already undergone resection; 192 patients (58%) underwent radiosurgery as primary treatment. The majority of patients (70%) harbored skull base tumors. The median tumor volume was 7.3 cm³ (range 0.5-50.5 cm³). The median tumor margin dose was 16 Gy (range 12-20 Gy). In 278 patients with 297 lesions the mean clinical and imaging follow-up period was 43 months (range 2-138 months). Two hundred seventy-eight tumors (94%) remained stable or decreased in size, and 19 tumors progressed in size. Factors associated with progression were tumor histological type and prior surgery. Treatment-related complications occurred in 8% of the patients and included cranial neuropathies, symptomatic edema, cyst formation, and stenosis of the internal carotid artery. In three patients (1%) tumor dedifferentiation was noted after SRS.

**CONCLUSIONS:**
Radiosurgical treatment of meningioma is safe and it has become the primary treatment for patients with small skull base tumors. Further study is needed to determine the long-term tumor control rates after such treatment, especially for patients treated with doses of 14 Gy or less.
OBJECT:
The authors sought to assess the respective roles of microsurgery and gamma knife surgery (GKS) in the treatment of patients with meningiomas.

METHODS:
The authors culled from a 4-year prospective database data on 74 cases of meningiomas. Thirty-eight were treated with GKS and 35 with microsurgery. Simpson Grade 1 or 2 resection was achieved in 86.1% of patients who underwent microsurgery. Patients who underwent GKS received a mean margin dose of 16.4 Gy (range 14-20 Gy). The mean tumor coverage was 94.7%, and the mean conformity index was 1.76. Significant differences between the two treatment groups (GKS compared with microsurgery) included age (mean 60 compared with 50.7 years), volume (mean 7.85 cm³ compared with 44.4 cm³), treatment history (55.3% compared with 14.3%), and tumor location (cavernous sinus/petroclival, 14 compared with three). The median follow up was 21.5 months (range 1.5-50 months). In patients with benign meningiomas GKS tumor control was 96.8% with one recurrence at the margin. The recurrence rate was zero of 27 for Simpson Grade 1 or 2 resection and three of four for higher grades in those patients who underwent microsurgery. There was no procedure-related mortality or permanent major neurological morbidity. The mean Karnofsky Performance Scale score was maintained for both forms of treatment. Symptoms improved in 48.4% of patients undergoing microsurgery and 16.7% of those who underwent GKS. Transient and permanent cranial nerve morbidity was 7.9 compared with 2.9%, and 5.3 compared with 8.5% for GKS and microsurgery, respectively. In a patient satisfaction survey 93.1% of microsurgery patients and 91.2% of GKS patients were highly satisfied.

CONCLUSIONS:
Both GKS and microsurgery serve important roles in the overall management of patients with meningiomas. Both are safe and effective and provide high degrees of satisfaction when used for differentially selected patients.
Natural history of petroclival meningiomas.
Van Havenbergh T, Carvalho G, Tatagiba M, Plets C, Samii M.
Department of Neurosurgery, University Hospital Antwerp, Antwerp, Belgium.
Tony.Van.Havenbergh@pandora.be

OBJECTIVE:
For evaluation of the natural history of petroclival meningiomas, a cooperative retrospective study of 21 conservatively treated patients is reported.

METHODS:
All patients had petroclival meningiomas that were observed for at least 4 years, with regular clinical and radiological control examinations. The follow-up periods ranged from 48 to 120 months (mean, 82 mo; median, 85 mo). Functional evaluations were performed by using the Karnofsky index. Individual growth curves and rates were defined.

RESULTS:
Age and sex distributions and presenting symptoms were comparable to those of other studies. During follow-up monitoring, radiological tumor growth was observed in 76% of the cases. With 63% of the growing tumors, there was functional deterioration. We performed statistical analyses of demographic features, radiological findings, and functional deterioration. Severe functional deterioration was observed to be statistically significantly associated with infratentorial growth and increased growth rates. A change in the growth pattern often preceded functional deterioration.

CONCLUSION:
This study provides a better understanding of the natural course of petroclival meningiomas. The growth patterns of these tumors are unpredictable and variable. The exact factors influencing growth remain unclear. This study can contribute to the optimization of individual management of these tumors.
Preservation of cranial nerve function following Gamma Knife radiosurgery for benign skull base meningiomas: experience in 121 patients with follow-up of 5 to 9.8 years.

Eustacchio S, Trummer M, Fuchs I, Schröttner O, Sutter B, Pendl G.

Department of Neurosurgery, Karl-Franzens University, Graz, Austria.

INTRODUCTION:
Microsurgical excision with preservation of juxtaposed neurovascular structures is considered the treatment of choice for skull base meningiomas, but there exists a great controversy regarding surgical resectability, potential risk for subsequent postoperative Cranial Nerve Deficit (CND) and the role of adjuvant or adjunctive treatment options. In this study we evaluated the effect of Gamma Knife Radiosurgery (GKRS) in 121 patients with benign basal meningiomas after a follow-up of 5 to 9.8 years.

METHODS:
Sixty patients had undergone open resections prior to radiosurgical treatment and 61 patients were treated by GKRS alone. Tumour volumes of 0.5 to 89.9 ccm (median 6.8 ccm) received a median marginal dose of 13 Gy (range 7-25 Gy) at the covering 25% to 80% isodose volume curves (median 45%).

RESULTS:
Neuroradiological controls demonstrated decreased tumour size in 73 patients (60.3%), stable meningioma volume in 47 cases (38.9%) and tumour enlargement in one patient (0.8%). Clinically, 54 patients (44.6%) improved and 61 cases (50.4%) remained unchanged. Four patients (3.3%) showed temporary and two patients (1.7%) permanent neurological deterioration (unrelated to tumour or treatment in one patient). Two patients (1.7%) developed radiation induced new or aggravated pre-existent CND (1 transient, 1 permanent) and two patients (1.7%) required further surgical resection.

CONCLUSION:
In our long-term experience, GKRS proved to be an attractive additional and save alternative primary treatment option in selected patients with basal meningiomas. The tumour control rate of 98.3% associated with excellent clinical outcome and low incidence for treatment related CND (1.7%) compares favourably with the reported microsurgical series.
Gamma knife radiosurgery in meningiomas of the posterior fossa. Experience with 62 treated lesions.

Department of Neurosurgery, University Hospital, Verona, Italy.

OBJECTIVES:
This study was undertaken to assess the role of the gamma knife (GK) in the treatment of meningiomas of the posterior cranial fossa (PCF) and to statistically analyze the predictability of arbitrarily-selected prognostic factors in such treatment.

METHODS:
From February 1993 to November 1998, 57 patients underwent GK treatment for 62 meningiomas of the PCF (19 M/38 F; average age, 57.5 years, ranging from 25 - 82 years). Tumor sites included: foramen jugular-petrous bone (26/62), petroclival (23/62), cerebellar convexity (6/62), tentorium (6/62), and foramen magnum (1/62). Single lesions were treated in 44/62 cases while meningiomatosis was treated in the remaining 18. Post-operative residual or recurrent tumor was found in 27/62 patients and, in 7/27, histology documented characteristics of biological aggressiveness (GII/III). Indications for radiosurgery included: advanced age, high operative risk, tumor volume < 20 ml, inoperable or refused for additional surgery. The prognostic factors statistically analyzed included: meningiomatosis (yes/no), radiosurgery as primary or adjuvant treatment, GI vs. GII/III histology, and tumor volume (< or = 5 ml vs. > 5 ml).

RESULTS:
The observation periods varied from 6 to 64.3 months (median 28.7 months). At the end of the study, 53/57 patients were alive and reported to be in stable or improved neurological condition. The cause of death for the remaining 4 patients included: 2 deaths associated with tumor progression, while 2 died due to causes unrelated to the disease. Neuroradiological evaluation documented the disappearance or reduction of the meningioma mass in 34/62 (55 %) cases, a stable imaging picture in 25/62 (40 %), and a progression only in 3/62 (5 %). To date, there have been no reported cases of post-GK permanent morbidity or mortality. Side effects observed were of a transient nature due to post-radiosurgical edema (6.5 %). With regard to statistical analysis, the only factor to appear to significantly influence efficacy of radiosurgery for tumor growth control (TGC) was the biological nature of the meningioma (chi(2) = 2.708). The presence of meningiomatosis, SR as a primary or adjuvant treatment, GI vs. GII/III histology, and tumor volume (< or = 5 ml vs. > 5 ml).

CONCLUSIONS:
The excellent results obtained for TGC with minimal associated side effects suggest that GK is an effective therapeutic tool also for treatment of PCF meningiomas.
Radiosurgery as alternative treatment for skull base meningiomas.
Pendl G, Eustacchio S, Unger F.

Department of Neurosurgery, Medical School and University, Graz, Austria.

The effect of radiosurgical treatment of skull base meningiomas in 197 patients with a follow-up of at least 2 years was evaluated. Ninety-two of these patients had combined surgical and radiosurgical treatment, while Gamma Knife Radiosurgery (GKRS) was performed as primary treatment in 105 patients. Follow-up was available in 164 patients with intervals of 25-97 months (median 55 months) after GKRS. The imaging controls revealed decreased tumour size in 84 patients (51%), stable tumour volume in 76 cases (47%) and increased tumour size in 4 cases (2%). Neurological examinations showed improved neurological status in 58 cases (35%), stable clinical status in 100 patients (61%) and slight worsening in 6 cases (4%). Due to excellent tumour control rate, good clinical outcome and a low complication rate GKRS represents not only an attractive additional treatment option for basal meningiomas, but may even replace microsurgery in selected cases. Copyright 2001 Harcourt Publishers Ltd.

Gamma knife radiosurgery of skull base meningiomas.

Department of Neurosurgery, University of Vienna Medical School, Austria.

BACKGROUND
The standard surgical treatment of meningiomas is total resection of the tumour. The complete removal of skull base meningiomas can be difficult because of the proximity of cranial nerves. Stereotactic radiosurgery (SRS) is an effective therapy, either for adjuvant treatment in case of subtotal or partial tumour resection, or as solitary treatment in asymptomatic meningiomas.

METHOD:
Between September 1992 and October 1995. SRS using the Leksell Gamma Knife was performed on 46 patients (f:m 35:15), ranging in age from 35 to 81 years, with skull base meningiomas at the Neurosurgical Department of the University of Vienna. According to the indication of gamma knife radiosurgery (GKRS) the patients (n = 46) were divided into two subgroups. Group I (combined procedure: subtotal resection followed by GKRS as a planned procedure or because of a recurrent meningioma), group II (GKRS as the primary treatment). Histological examination of tumour
tissue was available for 31 patients (67%) after surgery covering 25 benign (81%) and 6 malignant (19%) meningioma subtypes.

**FINDINGS:**
The overall tumour control rate after a mean follow-up period of 48 months (ranging from 36 to 76 months) was 96% (97.5% in benign and 83% in malignant meningiomas). Group I displayed a 96.7% tumour control rate, followed by group II with 93.3% respectively. Neurological follow-up showed an improvement in 33% stable clinical course in 58%) and a persistent deterioration of clinical symptoms in 9%. Remarkable neurological improvement after GKRS was observed in group II (47%), whereas in group I (26%) the amelioration of symptoms was less pronounced.

**INTERPRETATION:**
GKRS in meningiomas is a safe and effective treatment. A good tumour control and low morbidity rate was achieved in both groups (I, II) of our series, either as a primary or adjunctive therapeutic approach. The planned combination of microsurgery and GKRS extends the therapeutic spectrum in the treatment of meningiomas. Reduction of tumour volume, increasing the distance to the optical pathways and the knowledge of the actual growing tendency by histological evaluation of the tumour minimises the risk of morbidity and local regrowth. Small and sharply demarcated tumours are in general ideal candidates for single high dose-GKRS, even after failed surgery and radiation therapy, and in special cases also in larger tumour sizes with an adapted/reduced margin dose.

**J Neurosurg. 1999 Jul;91(1):44-50.**
Long-term outcomes after meningioma radiosurgery: physician and patient perspectives.
Kondziolka D, Levy EI, Niranjan A, Flickinger JC, Lunsford LD.

Department of Neurological Surgery, University of Pittsburgh, Pennsylvania 15213, USA.

**OBJECT:**
Stereotactic radiosurgery is a primary or adjuvant management approach used to treat patients with intracranial meningiomas. The goal of radiosurgery is long-term prevention of tumor growth, maintenance of the patient’s neurological function, and prevention of new neurological deficits. The object of this study is to report longer-term patient outcomes.

**METHODS:**
The authors evaluated 99 consecutive patients who underwent radiosurgery for meningioma between 1987 and 1992. Evaluation was performed using serial imaging tests, clinical evaluations, and a patient survey that was administered between 5 and 10 years after radiosurgery. Four patients underwent two radiosurgery procedures for separate meningiomas. The average tumor margin dose was 16 Gy and the median tumor volume was 4.7 ml (range 0.24-24 ml). Fifty-seven patients (57%) had undergone prior resection, of which 12 procedures were considered "total." Five patients received
fractionated radiation therapy before radiosurgery. Eighty-nine patients (89%) had skull base tumors. The clinical tumor control rate (no resection required) was 93%. Sixty-one (63%) of 97 tumors became smaller, 31 (32%) remained unchanged in size, and five (5%) were enlarged. Resection was performed in seven patients (7%), six of whom had undergone prior resection. New neurological deficits developed in five patients (5%) 3 to 31 months after radiosurgery. Twenty-seven (42%) of 65 responding patients were employed at the time of radiosurgery and 20 (74%) of these remained so. Radiosurgery was believed to have been "successful" by 67 of 70 patients who completed an outcomes questionnaire 5 to 10 years later. At least one complication was described by nine patients (14%) and in four patients the complications resolved.

CONCLUSIONS:
Five to 10 years after radiosurgery, 96% of surveyed patients believed that radiosurgery provided a satisfactory outcome for their meningioma. Overall, 93% of patients required no other tumor surgery. Incidences of morbidity in this early experience were usually transitory and relatively mild. Radiosurgery provided long-term tumor control associated with high rates of neurological function preservation and patient satisfaction.
4. Acoustic Neuroma

Acoustic Neuroma is a benign tumour located anatomically closely associated with the vestibular, the cochlear and the facial nerves. These tumours typically affect hearing and balance and can exert pressure on the brainstem with increasing volume. This explains the need for tumour control, but also the problems that arise when these benign tumours are surgically removed, because very often hearing cannot be preserved after open tumour resection and even the facial nerve can be endangered by surgery.

Gamma Knife is highly effective in stopping potential tumour growth while preserving normal postoperative facial function and hearing with low treatment associated side effects. The goal of every acoustic neuroma management is to provide the best outcome with the lowest possible risk level. The long-term results after radiosurgical treatment are comparable and often even superior to the best results with open microsurgical techniques. Tumour control was achieved in 96% of 1332 published patients in 6 studies.

Side effects in terms of transient facial and trigeminal nerve dysfunction are in fact rare. Symptoms related to facial nerve dysfunction occurred in 1.4% of the 1259 published cases treated by Gamma Knife. Hearing was preserved in ca 60% of 1259 patients in 5 studies. Chances to preserve functional hearing is significantly better following Gamma Knife compared to open surgery.

A recent study (Myrseth 2009) compared the outcome after treatment of acoustic neuroma with open surgical resection or Gamma Knife: No adverse events related to the Gamma Knife procedure were noted. Patients were routinely discharged the next day, and the sick leave form was restricted to the period of hospital stay. The mean hospital stay was 2.5 days (2–5 days) in the Gamma Knife group and 12.5 days (10–30 days) in the surgery group. Hearing was preserved in 17 out of 28 patients with functional hearing 2 years after Gamma Knife treatment, while hearing could not be preserved in any patient after open surgical resection (Myrseth 2009).

References (Gamma Knife in the Treatment of Metastases from Colo-rectal Carcinoma)
INTRODUCTION

Leksell Gamma Knife (LGK) radiosurgery is a safe and efficient therapeutic approach for vestibular schwannoma (VS) with low side effects. The goal of radiosurgery is not necessarily to cause significant tumour necrosis or to obtain a complete radiographic response, but to halt the tumour's growth permanently through its biological elimination. The 2 major aims of radiosurgery for VS are long-term tumour control and functional hearing preservation. The purpose of this study is to report our experience with LGK radiosurgery in the management of VS and to evaluate the hearing preservation rate after a minimum one-year follow-up.

MATERIAL AND METHODS

Between January 2000 and January 2011, 415 patients with unilateral VS underwent LGK radiosurgery at the University Erasmus Hospital of Brussels. There were 349 patients with previously untreated VS (86 grade I, 96 grade II, 141 grade III, 9 grade IVa, 17 unknown grades, according to Koos) and 66 patients with post-operative residual tumour. All patients in our series underwent evaluation with high resolution neurodiagnostic imaging including computed tomography and magnetic resonance imaging, and clinical evaluation as well as audiological tests that included tonal and speech audiometries. The Gardner Robertson (GR) classification is used to report the results of this study. We identified 276 patients treated for VS with LGK, tested and retested with speech and tonal audiometries by the same team, and followed for a minimum of one year.

RESULTS

Before LGK, 144 patients had serviceable (85 GR class I and 59 GR class II) hearing; 95 (65.97%) of these patients had preservation of serviceable hearing (Pure tone average $\leq 50$ db and Speech discrimination $> = 50\%$) at minimum one-year audiological follow-up. It was observed that 44 of the 85 GR class I patients (51.76%) maintained their level of audition and 66 of these (74.64%) preserved serviceable hearing. In the 34 patients with preradiosurgery non-serviceable hearing (GR class III-IV) 25 of these patients (73.52%) maintained their hearing. The tumour was stable or declining in size in 90.44% of cases.
CONCLUSION
LGK radiosurgery provides excellent tumour control in vestibular schwannomas and has low toxicity even after long-term follow-up.

Longitudinal assessment of quality of life and audiometric test outcomes in vestibular schwannoma patients treated with gamma knife surgery.
Park SS, Grills IS, Bojrab D, Pieper D, Kartush J, Maitz A, Martin A, Perez E, Hahn Y, Ye H, Martinez A, Chen P.
Department of Radiation Oncology, William Beaumont Hospital, Royal Oak, Michigan 48073, USA.

OBJECTIVE
To prospectively assess the quality of life (QOL) and hearing acuity in vestibular schwannoma (VS) patients after gamma knife surgery (GKS).

PATIENTS
Fifty-nine VS patients.

INTERVENTION:
GKS.

MAIN OUTCOME MEASURES
Prospective follow-up algorithm included 36-item Short Form Health Survey (SF-36), Hearing Handicap Inventory (HHI), Dizziness Handicap Inventory (DHI), Tinnitus Handicap Inventory (THI), pure-tone average, and speech discrimination hearing scores (Gardner-Robertson and American Academy of Otolaryngology), performed before and after GKS at 1-, 3-, 6-, 12-, and 18-month posttreatment intervals.

RESULTS
From December 2006 to November 2008, 59 VS patients were treated with a median follow-up of 15 months. At baseline, mean scores for SF-36, HHI, DHI, and THI were 73, 37, 17, and 23, respectively. Median baseline Gardner-Robertson and American Academy of Otolaryngology hearing acuity scores were 2 and B, respectively. No significant decline in SF-36 health survey was noted after GKS. Mean SF-36 score at baseline was 73, compared with a range of 70 to 77 at predetermined posttreatment intervals. Similarly, no significant changes in DHI, HHI, and THI were noted. Approximately 47% of patients with baseline serviceable hearing maintained serviceable hearing at 12 months. Significant acute and chronic worsening in hearing acuity were noted at 1 and 18 months, respectively. No correlative decline in QOL was noted as assessed by SF-36 or HHI.
CONCLUSION
No significant decline in global QOL occurred after GKS with relatively short follow-up and approximately 50% survey completion. When discussing therapy options with VS patients, anticipated treatment-related QOL outcomes should be considered.

Wait-and-see strategy compared with proactive Gamma Knife surgery in patients with intracanalicular vestibular schwannomas.
Régis J, Carron R, Park MC, Soumare O, Delsanti C, Thomassin JM, Roche PH.
Service de Neurochirurgie Stéréotaxique et Fonctionnelle, Centre Hospitalier Universitaire (C. H. U.) la Timone, AP-HM, Assistance Publique des Hôpitaux de Marseille, Marseille, France. jregis@ap-hm.fr

OBJECT
The roles of the wait-and-see strategy and proactive Gamma Knife surgery (GKS) in the treatment paradigm for small intracanalicular vestibular schwannomas (VSs) is still a matter of debate, especially when patients present with functional hearing. The authors compare these 2 methods.

METHODS
Forty-seven patients (22 men and 25 women) harboring an intracanalicular VS were followed prospectively. The mean age of the patients at the time of inclusion was 54.4 years (range 20-71 years). The mean follow-up period was 43.8 ± 40 months (range 9-222 months). Failure was defined as significant tumor growth and/or hearing deterioration that required microsurgical or radiosurgical treatment. This population was compared with a control group of 34 patients harboring a unilateral intracanalicular VS who were consecutively treated by GKS and had functional hearing at the time of radiosurgery.

RESULTS
Of the 47 patients in the wait-and-see group, treatment failure (tumor growth requiring treatment) was observed in 35 patients (74%), although conservative treatment is still ongoing for 12 patients. Treatment failure in the control (GKS) group occurred in only 1 (3%) of 34 patients. In the wait-and-see group, there was no change in tumor size in 10 patients (21%), tumor growth in 36 patients (77%), and a mild decrease in tumor size in 1 patient (2%). Forty patients in the wait-and-see group were available for a hearing level study, which demonstrated no change in Gardner-Robertson hearing class for 24 patients (60%). Fifteen patients (38%) experienced more than 10 db of hearing loss and 2 of them became deaf. At 3, 4, and 5 years, the useful hearing preservation rates were 75%, 52%, and 41% in the wait-and-see group and 77%, 70%, and 64% in the control group, respectively. Thus, the chances of maintaining functional hearing and avoiding further intervention were much higher in cases treated by GKS (79% and 60% at
2 and 5 years, respectively) than in cases managed by the wait-and-see strategy (43% and 14% at 2 and 5 years, respectively).

CONCLUSIONS
These data indicate that the wait-and-see policy exposes the patient to elevated risks of tumor growth and degradation of hearing. Both events may occur independently in the mid-term period. This information must be presented to the patient. A careful sequential follow-up may be adopted when the wait-and-see strategy is chosen, but proactive GKS is recommended when hearing is still useful at the time of diagnosis. This recommendation may be a main paradigm shift in the practice of treating intracanalicular VSs.

Long-term outcomes of Gamma Knife radiosurgery in patients with vestibular schwannomas.
Department of Radiation Oncology, Cleveland Clinic, Cleveland, Ohio 44195, USA.

Erratum in

OBJECT
The authors sought to determine the long-term tumor control and side effects of Gamma Knife radiosurgery (GKRS) in patients with vestibular schwannomas (VS).

METHODS
One hundred seventeen patients with VS underwent GKRS between January 1997 and February 2003. At the time of analysis, at least 5 years had passed since GKRS in all patients. The mean patient age was 60.9 years. The mean maximal tumor diameter was 1.77 ± 0.71 cm. The mean tumor volume was 1.95 ± 2.42 ml. Eighty-two percent of lesions received 1300 cGy and 14% received 1200 cGy. The median dose homogeneity ratio was 1.97 and the median dose conformality ratio was 1.78. Follow-up included MR imaging or CT scanning approximately every 6-12 months. Rates of progression to surgery were calculated using the Kaplan-Meier method.

RESULTS
Of the 117 patients in whom data were analyzed, 103 had follow-up MR or CT images and 14 patients were lost to follow-up. Fifty-three percent of patients had stable tumors and 37.9% had a radiographically documented response. Imaging-documented tumor progression was present in 8 patients (7.8%), but in 3 of these the lesion eventually stabilized. Only 5 patients required a neurosurgical intervention. The estimated 1-, 3-, and 5-year rates of progression to surgery were 1, 4.6, and 8.9%, respectively. One patient (1%) developed trigeminal neuropathy, 4 patients
(5%) developed permanent facial neuropathy, 3 patients (4%) reported vertigo, and 7 patients (18%) had new gait imbalance following GKRS.

**CONCLUSIONS**

Gamma Knife radiosurgery results in excellent local control rates with minimal toxicity for patients with VS. The authors recommend standardized follow-up to gain a better understanding of the long-term effects of GKRS.


Quality of life after gamma knife radiosurgery treatment in patients with a vestibular schwannoma: the patient's perspective.

Timmer FC, van Haren AE, Mulder JJ, Hanssens PE, van Overbeeke JJ, Cremers CW, Graamans K.

Department of Otorhinolaryngology, Head and Neck Surgery, Donders Institute for Brain, Cognition and Behavior, Radboud University Nijmegen Medical Center, PO BOX 9101, 6500 HB, Nijmegen, The Netherlands. f.timmer@kno.umcn.nl

This study evaluates the impact of gamma knife radiosurgery (GKRS) on the quality of life (QOL) of patients with a sporadic vestibular schwannoma (VS). This study pertains to 108 VS patients who had GKRS in the years 2003 through 2007. Two different QOL questionnaires were used: medical outcome study short form 36 (SF36) and Glasgow benefit inventory (GBI). Radiosurgery was performed using a Leksell 4C gamma knife. The results of the QOL questionnaires in relation to prospectively and retrospectively gathered data of the VS patients treated by GKRS. Eventually, 97 patients could be included in the study. Their mean tumor size was 17 mm (range 6-39 mm); the mean maximum dose on the tumor was 19.9 Gy (range 16-25.5 Gy) and the mean marginal dose on the tumor was 11.1 (range 9.3-12.5 Gy). SF36 scores showed results comparable to those for a normal Dutch population. GBI showed a marginal decline in QOL. No correlation was found between QOL and gender, age, tumor size, or radiation dose. Increased audiovestibular symptoms after GKRS were correlated with a decreased GBI score, and decreased symptoms were correlated with a higher QOL post-GKRS. **In this study shows that GKRS for VS has little impact on the general QOL of the VS patient.**

However, there is a wide range in individual QOL results. Individual QOL was influenced by the audiovestibular symptoms. No predictive patient, tumor, or treatment factors for QOL outcome after GKRS could be determined. Comparison with microsurgery is difficult because of intra group variability.
Predictors of hearing preservation after stereotactic radiosurgery for acoustic neuroma.
Kano H, Kondziolka D, Khan A, Flickinger JC, Lunsford LD.

Department of Neurological Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213, USA.

OBJECT
Many patients with acoustic neuromas (ANs) have hearing function at diagnosis and desire to maintain it. To date, radiosurgical techniques have been focused on conformal irradiation of the tumor mass, with less attention to inner ear structures for which there was scant radiobiological information. The authors of this study evaluated tumor control and hearing preservation as they relate to tumor volume, imaging characteristics, and nerve and cochlear radiation dose following stereotactic radiosurgery (SRS) using the Gamma Knife.

METHODS
Seventy-seven patients with ANs had serviceable hearing (Gardner-Robertson [GR] Class I or II) and underwent SRS between 2004 and 2007. This interval reflected more recent measurements of inner ear dosimetry during the authors' 21-year experience. The median patient age was 52 years (range 22-82 years). No patient had undergone any prior treatment for the ANs. The median tumor volume was 0.75 cm(3) (range 0.07-7.7 cm(3)), and the median radiation dose to the tumor margin was 12.5 Gy (range 12-13 Gy). At diagnosis, a greater distance from the lateral tumor to the end of the internal auditory canal correlated with better hearing function.

RESULTS
At a median of 20 months after SRS, no patient required any other additional treatment. Serviceable hearing was preserved in 71% of all patients and in 89% (46 patients) of those with GR Class I hearing. Significant prognostic factors for maintaining the same GR class included (all pre-SRS) GR Class I hearing, a speech discrimination score (SDS) ≥ 80%, a pure tone average (PTA) < 20 dB, and a patient age < 60 years. Significant prognostic factors for serviceable hearing preservation were (all pre-SRS) GR Class I hearing, an SDS ≥ 80%, a PTA < 20 dB, a patient age < 60 years, an intracanalicular tumor location, and a tumor volume < 0.75 cm(3). Patients who received a radiation dose of < 4.2 Gy to the central cochlea had significantly better hearing preservation of the same GR class. Twelve of 12 patients < 60 years of age who had received a cochlear dose < 4.2 Gy retained serviceable hearing at 2 years post-SRS.

CONCLUSIONS
As currently practiced, SRS with the Gamma Knife preserves serviceable hearing in the majority of patients. Tumor volume and anatomy relate to the hearing level before radiosurgery and influence technique. A low radiosurgical dose to the cochlea enhances hearing preservation.
OBJECTIVE
To conduct a prospective, open, nonrandomized study of treatment-associated morbidity in patients undergoing microsurgery or gamma knife radiosurgery (GKRS) for vestibular schwannomas.

METHODS

Ninety-one patients with vestibular schwannomas with a maximum tumor diameter of 25 mm in the cerebellopontine angle were treated according to a prospective protocol either by GKRS (63 patients) or open microsurgery (28 patients) using the suboccipital approach. Primary end points included hearing function, according to the Gardner-Robertson scale, and facial nerve function, according to the House-Brackmann scale at 2 years. Clinical data included a balance platform test, score for tinnitus and vertigo using a visual analog scale, and working ability. Patients responded to the quality-of-life questionnaires Short-Form 36 and Glasgow Benefit Inventory.

RESULTS

Three elderly GKRS patients withdrew; all remaining patients were followed for 2 years. Both primary end points were highly significant in favor of GKRS (P < 0.001). Evidence of reduced facial nerve function (House-Brackmann grade 2 or poorer) at 2 years was found in 13 of 28 open microsurgery patients and 1 of 60 GKRS patients. Thirteen of 28 patients who underwent surgery had serviceable hearing (Gardner-Robertson grade A or B) preoperatively, but none had serviceable hearing postoperatively. Twenty-five of 60 GKRS patients had serviceable hearing before treatment, and 17 (68%) of them had serviceable hearing 2 years after treatment. The tinnitus and vertigo visual analog scale score, as well as balance platform tests, did not change significantly after treatment, and working status did not differ between the groups at 2 years. Quality of life was significantly better in the GKRS group at 2 years, based on the Glasgow Benefit Inventory questionnaire. One GKRS patient required operative treatment within the 2-year study period.

CONCLUSION
This is the second prospective study to demonstrate better facial nerve and hearing outcomes from GKRS than from open surgery for small- and medium-sized vestibular schwannomas.
Neurosurgery. 2009 Feb;64(2):289-96; discussion 296.

Hearing preservation after gamma knife radiosurgery for vestibular schwannomas presenting with high-level hearing.

Tamura M, Carron R, Yomo S, Arkha Y, Muraciolle X, Porcheron D, Thomassin JM, Roche PH, Régis J.

Department of Stereotactic and Functional Neurosurgery, Hôpital de la Timone, Marseille, France.

OBJECTIVE

The aim of this study was to evaluate long-term hearing preservation after gamma knife radiosurgery (GKS) for vestibular schwannomas in patients with initially normal or subnormal hearing (Gardner-Robertson Class 1) and to determine the predictive factors for functional hearing preservation.

METHODS

Since July 1992, more than 2053 vestibular schwannomas have been treated by GKS and followed at the Timone University Hospital, Marseille. A minimum of 3 years of follow-up (range, 3-11 years; median, 48 months) is available for 74 patients (without neurofibromatosis Type 2 or previous surgery) with Gardner-Robertson Class 1 hearing.

RESULTS

The average age of the patients was 47.5 years (range, 17-76 years). The number of tumors in Koos Stage I was 8, the average number in Stage II was 21, the average number in Stage III was 43, and the average number in Stage IV was 2. The median number of isocenters was 8 (range, 2-45), and the median marginal dose was 12 Gy (range, 9-13 Gy). At the time of the last follow-up evaluation, 78.4% of the patients had preserved functional hearing. Tumor control was achieved in 93% of the cases. The probability of preserving functional hearing was higher in patients who had an initial symptom other than hearing decrease (91.1%), in patients younger than 50 years (83.7%), and in those treated with a dose to the cochlea of less than 4 Gy (90.9%).

CONCLUSION

This study shows that the probability of preserving functional hearing in the long term after GKS for patients presenting with unilateral vestibular schwannomas is very high. The positive predictive factors appear to be young age, an initial symptom other than hearing decrease, and a low dose to the cochlea.
**INTRODUCTION**

The majority of patients still lose the functionality of their hearing in spite of the technical advances in microsurgery. Our aim was to evaluate the hearing preservation potential of Gamma Knife Surgery. We have reviewed our experience and the literature in order to evaluate the probability to obtain such functional preservation and the factors influencing it.

**METHODS**

Since July 1992, 2,053 patients have been operated on by Gamma Knife Radiosurgery in Timone University Hospital. This population included 184 unilateral schwannoma patients with functional preoperative hearing (Gardner-Robertson 1 or 2) treated by first intention radiosurgery with a marginal dose lower than 13 Gy. The population included 74 patients with subnormal hearing (class 1). All have been studied with a follow-up longer than 3 years. Univariate and multivariate analyses have been carried out.

**RESULTS**

Numerous parameters greatly influence the probability of functional hearing preservation at 3 years, which is globally 60%. The main preoperative parameters of predictability are limited hearing loss that is Gardner-Robertson stage 1 (vs. 2), presence of tinnitus, young age of the patient and small size of the lesion. The **functional hearing preservation at 3 years is 77.8% when the patient is initially in stage 1, 80% in patients with tinnitus as a first symptom and 95% when the patient has both**. In these patients, the probability of functional preservation at 5 years is 84%.

Comparison of these results with the main series of the literature confirms the reproducibility of our results. Additionally, we have demonstrated a higher chance of hearing preservation when the dose to the cochlea is lower than 4 Gy.

**CONCLUSION**

We report a large population of patients treated by radiosurgery with functional preoperative hearing. These results demonstrate the possibility to preserve functional hearing in a high percentage of selected patients. Radiosurgery offers them a higher chance of functional hearing preservation than microsurgery or simple follow-up.

Facial nerve function insufficiency after radiosurgery versus microsurgery.

Tamura M, Murata N, Hayashi M, Roche PH, Régis J.

Stereotactic and Functional Neurosurgery, Timone University Hospital, 264 boulevard Saint Pierre, Marseille Cedex 05, France.

**BACKGROUND**

Due to the synergic role of the facial nerve and the nervus intermedius in the mechanical protection of the eye and taste, vestibular schwannomas and/or their treatment may prove to be dangerous for the visual function and taste. Our goal was to evaluate and compare the impact of the tumor itself and the impact of microsurgery (MS) or Gamma Knife radiosurgery (GKS).

**MATERIALS AND METHODS**

A functional questionnaire evaluating, among other items, patient complaints related to the eye and taste has been **given out to a series of 200 patients 3 years after the GKS of a unilateral vestibular schwannoma not previously resected.** Their answers were compared with those of a group of 200 patients operated on microsurgically. A Schirmer test was additionally performed before radiosurgery (RS) and more than 2 years after RS in 66 patients. Results: The risk of dry eye and burning eye is much **higher in patients operated by MS compared to patients operated by GKS due to the high incidence of facial palsy (FP) in the former (57/99) and its absence in the later (0/80).** In the population operated on microsurgically, the presence of a permanent FP (57 patients among 99 responding to the questionnaire) was, of course, associated with a high rate of complaint, with burning eye in 27 and crying eye in 39. In patients from the two arms with no FP, a dry eye was reported in 8/64 after GKS and 7/42 after MS (not significant) and a burning eye in 9/64 after GKS and 9/42 after MS (not significant). Thus, 14% of patients with no clinical signs of impairment of the VIIth motor nerve presented signs indicating the injury of the intermedius nerve, with the same probability whatever the kind of surgery. When no permanent FP was observed, a crocodile tear syndrome was more frequently observed after MS (4/42 versus 1/64; p = 0.07). This suggests an early lesion of the VIIth motor nerve and nervus intermedius and a subsequent abnormal regrowth. The only patient reporting a crocodile tear syndrome after GKS turned out to have a transiently presented mild deficit of the orbicular muscle signing a transient partial facial nerve injury. In the absence of FP, a 'crying eye' was reported more frequently after MS (16/42 vs. 9/64; p = 0.01) leading us to suspect a frequent subclinical injury of the VIIth nerve in those patients operated on using MS with no obvious FP. Patients tested with the Schirmer test before and more than 2 years later were improved in 27.3%, stable in 56.1% and worse in 16.7% of cases. The answers about taste showed that 8.1% of patients after GKS and 45.5% of patients after MS complained of taste.
CONCLUSIONS
This study is the first demonstrating that RS can induce nervus intermedius injury in a small percentage of cases (14%). These patients have been treated 11 years ago with what we can consider as 'archeo-GKS technology' compared to today's radiosurgical instruments. Influence of modern GKS on the nervus intermedius is currently under evaluation in our group. However, symptoms related to the eye and taste either due to the injury of the nervus intermedius or the VIIth motor nerve or both are much more frequent after MS than after RS.

The wait and see strategy for intracanalicular vestibular schwannomas.
Roche PH, Soumare O, Thomassin JM, Régis J.
Service de Neurochirurgie, Hôpital Sainte-Marguerite, Assistance Publique-Hopitaux de Marseille, Marseille, France. proche@mail.ap-hm.fr

To refine our therapeutic policy for intracanalicular tumors, we reviewed our series of patients who where initially treated conservatively. Forty-seven patients (22 men and 25 women) harboring an intracanalicular vestibular schwannoma were followed prospectively. Mean age at the time of inclusion was 54.4 (20-71) years. The mean follow-up period was 43.8 months (+/-40 months) ranging from 9 to 222 months. Failure was defined as significant tumor growth and/or hearing deterioration that required a microsurgical or radiosurgical treatment. Failure was observed in 35 cases while a conservative treatment is still ongoing in 12 patients. Ten patients kept an unchanged tumor size (21.3%), while 36 patients experienced a tumor growth (76.6%), and 1 patient experienced a mild decreased tumor size (2.1%). Among the 40 patients who where available for hearing level study, 24 patients (60%) did not change their Gardner and Robertson hearing class. Fifteen patients (37.5%) experienced a >10-dB hearing loss and 2 of them became deaf. One patient (2.5%) improved her hearing level from 56.3 to 43.8 dB over a 39.5-month follow-up period. These data suggest that the wait and see policy exposes the patient to degradation of hearing and tumor growth. Both events may occur in an independent way in the middle-term period. This information has to be given to the patient, and a careful sequential follow-up may be adopted when the wait and see strategy is chosen.
Hearing preservation after stereotactic radiosurgery for vestibular schwannoma: a systematic review.

Yang I, Aranda D, Han SJ, Chennupati S, Sughrue ME, Cheung SW, Pitts LH, Parsa AT.

Department of Neurological Surgery, University of California at San Francisco, 505 Parnassus Avenue, San Francisco, California 94143, USA.

Radiosurgery has evolved into an effective alternative to microsurgical resection in the treatment of patients with vestibular schwannoma. We performed a systematic analysis of the literature in English on the radiosurgical treatment of vestibular schwannoma patients. A total of 254 published studies reported assessable and quantifiable outcome data of patients undergoing radiosurgery for vestibular schwannomas. American Association of Otolaryngology-Head and Neck Surgery (AAO-HNS) class A or B and Gardner-Robertson (GR) classification I or II were defined as having preserved hearing. A total of 5825 patients (74 articles) met our inclusion criteria. Practitioners who delivered an average dose of 12.5 Gy as the marginal dose reported having a higher hearing preservation rate (12.5 Gy=59% vs. >12.5 Gy=53%, p=0.0285). Age of the patient was not a significant prognostic factor for hearing preservation rates (<65 years=58% vs. >65 years=62%; p=0.4317). The average overall follow-up was 41.2 months. Our data suggest that an overall hearing preservation rate of about 57% can be expected after radiosurgical treatment, and patients treated with 12.5 Gy were more likely to have preserved hearing.

Predictors of hearing preservation after stereotactic radiosurgery for acoustic neuroma.

Kano H, Kondziolka D, Khan A, Flickinger JC, Lunsford LD.

Department of Neurological Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213, USA.

OBJECT

Many patients with acoustic neuromas (ANs) have hearing function at diagnosis and desire to maintain it. To date, radiosurgical techniques have been focused on conformal irradiation of the tumor mass, with less attention to inner ear structures for which there was scant radiobiological information. The authors of this study evaluated tumor control and hearing preservation as they relate to tumor volume, imaging characteristics, and nerve and cochlear radiation dose following stereotactic radiosurgery (SRS) using the Gamma Knife.

METHODS
Seventy-seven patients with ANs had serviceable hearing (Gardner-Robertson [GR] Class I or II) and underwent SRS between 2004 and 2007. This interval reflected more recent measurements of inner ear dosimetry during the authors' 21-year experience. The median patient age was 52 years (range 22-82 years). No patient had undergone any prior treatment for the ANs. The median tumor volume was 0.75 cm(3) (range 0.07-7.7 cm(3)), and the median radiation dose to the tumor margin was 12.5 Gy (range 12-13 Gy). At diagnosis, a greater distance from the lateral tumor to the end of the internal auditory canal correlated with better hearing function.

RESULTS
At a median of 20 months after SRS, no patient required any other additional treatment. Serviceable hearing was preserved in 71% of all patients and in 89% (46 patients) of those with GR Class I hearing. Significant prognostic factors for maintaining the same GR class included (all pre-SRS) GR Class I hearing, a speech discrimination score (SDS) >or= 80%, a pure tone average (PTA) < 20 dB, and a patient age < 60 years. Significant prognostic factors for serviceable hearing preservation were (all pre-SRS) GR Class I hearing, an SDS >or= 80%, a PTA < 20 dB, a patient age < 60 years, an intracanalicular tumor location, and a tumor volume < 0.75 cm(3). Patients who received a radiation dose of < 4.2 Gy to the central cochlea had significantly better hearing preservation of the same GR class. Twelve of 12 patients < 60 years of age who had received a cochlear dose < 4.2 Gy retained serviceable hearing at 2 years post-SRS.

CONCLUSIONS
As currently practiced, SRS with the Gamma Knife preserves serviceable hearing in the majority of patients. Tumor volume and anatomy relate to the hearing level before radiosurgery and influence technique. A low radiosurgical dose to the cochlea enhances hearing preservation.

IMPORTANT
Neurosurgery. 2009 Apr;64(4):654-61; discussion 661-3.

Department of Neurosurgery, Haukeland University Hospital, Bergen, Norway.

OBJECTIVE
To conduct a prospective, open, nonrandomized study of treatment-associated morbidity in patients undergoing microsurgery or gamma knife radiosurgery (GKRS) for vestibular schwannomas.

METHODS
Ninety-one patients with vestibular schwannomas with a maximum tumor diameter of 25 mm in the cerebellopontine angle were treated according to a prospective protocol either
by GKRS (63 patients) or open microsurgery (28 patients) using the suboccipital approach. Primary end points included hearing function, according to the Gardner-Robertson scale, and facial nerve function, according to the House-Brackmann scale at 2 years. Clinical data included a balance platform test, score for tinnitus and vertigo using a visual analog scale, and working ability. Patients responded to the quality-of-life questionnaires Short-Form 36 and Glasgow Benefit Inventory.

RESULTS
Three elderly GKRS patients withdrew; all remaining patients were followed for 2 years. Both primary end points were highly significant in favor of GKRS (P < 0.001). Evidence of reduced facial nerve function (House-Brackmann grade 2 or poorer) at 2 years was found in 13 of 28 open microsurgery patients and 1 of 60 GKRS patients. Thirteen of 28 patients who underwent surgery had serviceable hearing (Gardner-Robertson grade A or B) preoperatively, but none had serviceable hearing postoperatively. Twenty-five of 60 GKRS patients had serviceable hearing before treatment, and 17 (68%) of them had serviceable hearing 2 years after treatment. The tinnitus and vertigo visual analog scale score, as well as balance platform tests, did not change significantly after treatment, and working status did not differ between the groups at 2 years. Quality of life was significantly better in the GKRS group at 2 years, based on the Glasgow Benefit Inventory questionnaire. One GKRS patient required operative treatment within the 2-year study period. CONCLUSION: This is the second prospective study to demonstrate better facial nerve and hearing outcomes from GKRS than from open surgery for small- and medium-sized vestibular schwannomas.

Management of large vestibular schwannomas by combined surgical resection and gamma knife radiosurgery.
Service de Neurochirurgie Fonctionnelle et Stéréotaxique, Hôpital d’Adulte de la Timone, 264 boulevard Saint Pierre, Marseille Cedex 05, France.

In this report, we evaluated the treatment results of a combination of surgery and radiosurgery for large vestibular schwannomas. The series of 8 patients included in this study underwent surgery followed by radiosurgical treatment between January 2000 and January 2006. The patients included 5 males and 3 females aged 24-78 years (mean age: 53 years). The average maximum diameter of the tumor was 40 (35-45) mm. At the time of radiosurgery, the treatment size became 18 (9-20) mm. The mean peripheral dose administered was 11.8 (range 11-13) Gy, and the mean dose administered in the centre of the tumor was 23.75 (22-26) Gy. The mean follow-up period was 46 months after radiosurgery. Excellent facial nerve function (House-Brackmann grade 1 or 2) was
preserved in 7/8 patients (87.5%). In the case of large vestibular schwannomas, the combined management is one option for maintaining cranial nerve function and tumor growth control.

**J Neurosurg. 2005 Jan;102 Suppl:204-6.**

Increased preservation of functional hearing after gamma knife surgery for vestibular schwannoma.
van Eck AT, Horstmann GA.

Gamma Knife Centre Krefeld, Krefeld, Germany. vaneck@gamma-knife.de

**OBJECT**

Gamma knife surgery (GKS) for vestibular schwannoma is still associated with an additional hearing loss of approximately 30%. The purpose of this study was to record the effect on hearing preservation of maintaining a margin dose of 13 Gy while reducing the maximum dose to 20 Gy.

**METHODS**

Seventy-eight of 95 patients who entered a prospective protocol with a follow up of at least 12 months (mean 22 months) were evaluated. The mean tumor volume was 2.28 cm³. After a mean follow-up duration of 22 months, the magnetic resonance imaging-based tumor control rate was 87%. In two cases a second procedure (surgery) was necessary. Thus, the clinical control rate was 97.5%. In two cases there was an increase in trigeminal dysesthesia. One patient suffered transient facial nerve impairment. Functional hearing was preserved in 83.4% of the patients with functional hearing preoperatively.

**CONCLUSIONS**

Reducing the maximum dose to 20 Gy seems to be an effective treatment, which probably increases preservation of functional hearing without sacrificing the high tumor control rates achieved in radiosurgery. Postradiosurgery tumor swelling occurred in 25% of the cases and was not correlated with hearing deterioration.

**IMPORTANT**


Radiosurgery of vestibular schwannomas: summary of experience in 829 cases.
Lunsford LD, Niranjan A, Flickinger JC, Maitz A, Kondziolka D.

Department of Neurological Surgery and Radiation Oncology, The University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213, USA. lunsfordld@upmc.edu

**OBJECT**
Management options for vestibular schwannomas (VSs) have greatly expanded since the introduction of stereotactic radiosurgery. Optimal outcomes reflect long-term tumor control, preservation of cranial nerve function, and retention of quality of life. The authors review their 15-year experience.
METHODS
Between 1987 and 2002, some 829 patients with VSs underwent gamma knife surgery (GKS). Dose selection, imaging, and dose planning techniques evolved between 1987 and 1992 but thereafter remained stable for 10 years. The average tumor volume was 2.5 cm³. The median margin dose to the tumor was 13 Gy (range 10-20 Gy). No patient sustained significant perioperative morbidity. The average duration of hospital stay was less than 1 day. Unchanged hearing preservation was possible in 50 to 77% of patients (up to 90% in those with intracanalicular tumors). Facial neuropathy risks were reduced to less than 1%. Trigeminal symptoms were detected in less than 3% of patients whose tumors reached the level of the trigeminal nerve. Tumor control rates at 10 years were 97% (no additional treatment needed).

CONCLUSIONS
Superior imaging, multiple isocenter volumetric conformal dose planning, and optimal precision and dose delivery contributed to the long-term success of GKS, including in those patients in whom initial microsurgery had failed. Gamma knife surgery provides a low risk, minimally invasive treatment option for patients with newly diagnosed or residual VS. Cranial nerve preservation and quality of life maintenance are possible in long-term follow up.

Low-dose radiosurgery for large vestibular schwannomas: long-term results of functional preservation.
Inoue HK.
Restorative Neurosurgery, Institute of Neural Organization, Kobayashi, Fujioka, Gunma Prefecture, Japan. chair.ino@instno-med.org

OBJECT:
The author conducted a study to assess the long-term results obtained in patients who underwent GKS for large vestibular schwannomas (> 3 cm in diameter). Facial and cochlear nerve functions were evaluated.

METHODS:
Twenty consecutive large tumors in 18 patients (including two cases of neurofibromatous Type 2 [NF2]) were followed for more than 6 years. There were eight tumors that were more than 4 cm in maximum diameter. Microsurgery had already been performed prior to GKS in 11 patients (nine recurrent and two residual tumors). Four patients (including one with NF2) died during the follow-up period of other diseases or by accident. Fourteen of 15 tumors were stable or decreased in size. Microsurgery was performed in one patient 2 years after radiosurgery. Facial nerve function was preserved in all patients and hearing preserved in
four of five patients with cochlear nerve function prior to radiosurgery. No adverse effects of radiosurgery have been observed to date.

CONCLUSIONS:
Gamma knife surgery seems to have a place in the low-dose treatment of selected large vestibular schwannoma in patients with a reasonable chance of retaining facial function and pretreatment hearing level. Patients with severe brainstem compression should first be undergo microsurgery.

Gamma knife surgery for vestibular schwannoma: 10-year experience of 195 cases.
Chung WY, Liu KD, Shiau CY, Wu HM, Wang LW, Guo WY, Ho DM, Pan DH.

Department of Neurosurgery (Cancer Center), Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan, Republic of China. wychung@vghtpe.gov.tw

OBJECT
The authors conducted a study to determine the optimal radiation dose for vestibular schwannoma (VS) and to examine the histopathology in cases of treatment failure for better understanding of the effects of irradiation.

METHODS
A retrospective study was performed of 195 patients with VS; there were 113 female and 82 male patients whose mean age was 51 years (range 11-82 years). Seventy-two patients (37%) had undergone partial or total excision of their tumor prior to gamma knife surgery (GKS). The mean tumor volume was 4.1 cm$^3$ (range 0.04-23.1 cm$^3$). Multiisocenter dose planning placed a prescription dose of 11 to 18.2 Gy on the 50 to 94% isodose located at the tumor margin. Clinical and magnetic resonance (MR) imaging follow-up evaluations were performed every 6 months. A loss of central enhancement was demonstrated on MR imaging in 69.5% of the patients. At the latest MR imaging assessment decreased or stable tumor volume was demonstrated in 93.6% of the patients. During a median follow-up period of 31 months resection was avoided in 96.8% of cases. Uncontrolled tumor swelling was noted in five patients at 3.5, 17, 24, 33, and 62 months after GKS, respectively. Twelve of 20 patients retained serviceable hearing. Two patients experienced a temporary facial palsy. Two patients developed a new trigeminal neuralgia. There was no treatment-related death. Histopathological examination of specimens in three cases (one at 62 months after GKS) revealed a long-lasting radiation effect on vessels inside the tumor.

CONCLUSIONS
Radiosurgery had a long-term radiation effect on VSs for up to 5 years. A margin 12-Gy dose with homogeneous distribution is effective in preventing tumor progression, while posing no serious threat to normal cranial nerve function.
IMPORTANT LONG TERM FU


Long-term outcomes in patients with vestibular schwannomas treated using gamma knife surgery: 10-year follow up.

Hasegawa T, Kida Y, Kobayashi T, Yoshimoto M, Mori Y, Yoshida J.

Department of Neurosurgery, Gamma Knife Center, Komaki City Hospital, Komaki, Japan. h-toshi@komakihp.gr.jp

OBJECT

Gamma knife surgery (GKS) has been a safe and effective treatment for vestibular schwannomas in both the short and long term, although less is known about long-term outcomes in the past 10 years. The aim of this study was to clarify long-term outcomes in patients with vestibular schwannomas treated using GKS based on techniques in place in the early 1990s.

METHODS:

Eighty patients harboring a vestibular schwannoma (excluding neurofibromatosis Type 2) were treated using GKS between May 1991 and December 1993. Among these, 73 patients were assessed; seven were lost to follow up. The median duration of follow up was 135 months. The mean patient age at the time of GKS was 56 years old. The mean tumor volume was 6.3 cm³, and the mean maximal and marginal radiation doses applied to the tumor were 28.4 and 14.6 Gy, respectively. Follow-up magnetic resonance images were obtained in 71 patients. Forty-eight patients demonstrated partial tumor remission, 14 had tumors that remained stable, and nine demonstrated tumor enlargement or radiation-induced edema requiring resection. Patients with larger tumors did not fare as well as those with smaller lesions. The actuarial 10-year progression-free survival rate was 87% overall, and 93% in patients with tumor volumes less than 10 cm³. No patient experienced malignant transformation.

CONCLUSIONS:

Gamma knife surgery remained an effective treatment for vestibular schwannomas for longer than 10 years. Although treatment failures usually occurred within 3 years after GKS, it is necessary to continue follow up in patients to reveal delayed tumor recurrence.


Acoustic neuroma radiosurgery with marginal tumor doses of 12 to 13 Gy.


Department of Radiation Oncology, Joint Radiation Oncology Center, University of Pittsburgh School of Medicine, 200 Lothrop Street, Pittsburgh, PA 15213, USA. jflickin@pitt.edu
PURPOSE
To define tumor control and clinical outcomes of radiosurgery to marginal tumor doses of 12-13 Gy for unilateral acoustic neuroma patients.

METHODS AND MATERIALS:
Three hundred thirteen patients with previously untreated unilateral acoustic neuromas (vestibular schwannomas) underwent gamma knife radiosurgery between February 1991 and February 2001 with marginal tumor doses of 12-13 Gy (median, 13 Gy). Median follow-up was 24 months (maximum, 115 months; 36 patients with > or =60 months). Maximum doses were 20-26 Gy (median, 26 Gy), and treatment volumes were 0.04-21.4 mL (median, 1.1 mL).

RESULTS:
The actuarial 6-year clinical tumor control rate (no requirement for surgical intervention) for the entire series was 98.6 +/- 1.1%. Two patients required tumor resection; one had a complete resection for solid tumor growth and one required partial resection for an enlarging adjacent subarachnoid cyst. Six-year actuarial rates for preservation of facial nerve function, normal trigeminal nerve function, unchanged hearing level, and useful hearing were 100%, 95.6 +/- 1.8%, 70.3 +/- 5.8%, and 78.6 +/- 5.1%, respectively. The risk of developing trigeminal neuropathy correlated with increasing tumor volume (p = 0.038).

CONCLUSIONS:
Acoustic neuroma radiosurgery with doses of 12-13 Gy provides high rates of tumor control and cranial nerve preservation.

[Functional outcomes of radiosurgical treatment of vestibular schwannomas: 1000 successive cases and review of the literature]
[Article in French]
Regis J, Delsanti C, Roche PH, Thomassin JM, Pellet W.
Groupe d'Otoneurochirurgie, Hopital Universitaire de La Timone, Marseille. jregis@ap-hm.fr

RATIONALE
To evaluate the functional results of Gamma Knife surgery of vestibular schwannomas relying on a large and prospective series of consecutive cases.

MATERIAL AND METHOD
The first 1000 patients with cerebello-pontine angle schwannomas were consecutively treated by Gamma Knife in Marseille Timone University Hospital between July 1992 and March 2001. Patients without NF2 and or clinico-radiological arguments in favor of a facial origin accounted for
a population of 927 patients (414 males, for 513 females) including 843 treated in first intention. In this series the Koos classification was: stage I 77 patients, stage II 520 patients, stage III 287 patients and stage IV 42 patients. The average Volume was 12.7mm3. Haring was usefull (Gardner and Robertson) before radiosurgery in 47% of the patients (subnormal in 20.3%).

RESULTS
Tumor control at last follow-up was 97%. Globally, a clinical trigeminal injury was observed in 0.6% of the patients and a facial palsy in 1.3%. There was clearly a decrease of the incidence of neuropathies with time; no facial palsy being reported among the last 258 patients. The rate of functional hearing preservation (Gardner) for patients initially in class I was 77.8% (47.6% for class II) at 3 Years. This rate of functional preservation reached 95% among patients with tinnitus as a first symptom.

CONCLUSION
Today, strong evidence surports the superiority of Gamma Knife surgery in term of functional preservation and equal efficacy compared with microsurgical removal. Consequently, radiosurgery must be preferred as a first intention choice for young patients with few symptoms presenting with a small to middle size vestibular schwannomas (Koos I-III).

Conservative management, gamma-knife radiosurgery, and microsurgery for acoustic neurinomas: a systematic review of outcome and risk of three therapeutic options.
Yamakami I, Uchino Y, Kobayashi E, Yamaura A.
Department of Neurosurgery, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chuoku, Chiba, Japan 260-8670. yamakami@med.m.chiba-u.ac.jp

Conservative management, gamma-knife (GK) radiosurgery, and microsurgery are therapeutic options for acoustic neurinomas (ANs). To determine the outcomes and risks of these methods this systematic review analyzed data from 903 patients with conservative management, 1475 with GK radiosurgery, and 5005 with microsurgery from 38 studies identified in MEDLINE searches. Conservative management over a 3.1-year period showed that 51% of ANs showed a tumor growth, an average tumor growth rate was 1.87 mm year-1, 20% of ANs ultimately required surgical intervention, and a third of the patients lost useful hearing. GK radiosurgery significantly reduced the percentage of ANs that enlarged, to 8%, and reduced the percentage that underwent microsurgery to 4.6% over a 3.8-year period. Microsurgery removed 96% of ANs totally, with tumor recurrence, mortality, and major disability rates of 1.8%, 0.63%, and 2.9%, respectively. The majority of ANs grow slowly, but ultimately require intervention. Carrying the risk of hearing loss, conservative management should be supplemented with close follow-up. With a low
rate of morbidity, GK radiosurgery suppresses tumor growth and provides good tumor control. Microsurgery provides the best tumor control, although mortality and morbidity are not completely eliminated.


Long-term results after radiosurgery for benign intracranial tumors.
Kondziolka D, Nathoo N, Flickinger JC, Niranjan A, Maitz AH, Lunsford LD.

Departments of Neurological Surgery and Radiation Oncology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA. kondziolkads@msx.upmc.edu

**BACKGROUND**
Stereotactic radiosurgery is the principal therapeutic alternative to resecting benign intracranial tumors. The goals of radiosurgery are the long-term prevention of tumor growth, the maintenance of patient function, and the prevention of new neurological deficits or adverse radiation effects. Evaluation of long-term outcomes more than 10 years after radiosurgery is needed.

**METHODS:**
We evaluated 285 consecutive patients who underwent radiosurgery for benign intracranial tumors between 1987 and 1992. Serial imaging studies were obtained, and clinical evaluations were performed. Our series included 157 patients with vestibular schwannomas, 85 patients with meningiomas, 28 patients with pituitary adenomas, 10 patients with other cranial nerve schwannomas, and 5 patients with craniopharyngiomas. Prior surgical resection had been performed in 44% of these patients, and prior radiotherapy had been administered in 5%. The median follow-up period was 10 years.

**RESULTS:**
Overall, 95% of the 285 patients in this series had imaging-defined local tumor control (63% had tumor regression, and 32% had no further tumor growth). The actuarial tumor control rate at 15 years was 93.7%. In 5% of the patients, delayed tumor growth was identified. Resection was performed after radiosurgery in 13 patients (5%). No patient developed a radiation-induced tumor. Eighty-one percent of the patients were still alive at the time of this analysis. Normal facial nerve function was maintained in 95% of patients who had normal function before undergoing treatment for acoustic neuromas.

**CONCLUSION:**
Stereotactic radiosurgery provided high rates of tumor growth control, often with tumor regression, and low morbidity rates in patients with benign intracranial tumors when evaluated over the long term. This study supports radiosurgery as a reliable alternative to surgical resection for selected patients with benign intracranial tumors.

Surgery combined with radiosurgery of large acoustic neuromas.
Iwai Y, Yamanaka K, Ishiguro T.

Department of Neurosurgery, Osaka City General Hospital, Osaka, Japan.

The treatment of acoustic neuromas has been improved by advancements in microsurgical techniques and in radiosurgery. To further elucidate the degree of clinical improvement, we evaluated the treatment results of a combination of surgery and radiosurgery for large acoustic neuromas.

METHODS:
From January 1994 through December 2000, we treated 14 patients with large acoustic neuromas using a combination of surgery and radiosurgery. Of these, 8 were male and 6 were female patients, with an average age of 47 years (range, 18-64). The average maximum diameter of the tumor was 42 mm (range, 30-58 mm). All patients underwent operations using the retrosigmoid approach, and one patient was retreated using the transpetrosal transtentorial approach. The tumors were removed subtotally in thirteen patients and partially in one who had a very large hypervascular acoustic neuroma. There were no mortality and no surgical complications, such as hemorrhage or CSF leakage. Postoperative facial palsy was avoided in 10 patients (71%). Radiosurgery was performed 1 to 6 months (mean, 2.9 months) after surgery. At the time of radiosurgery, the treatment size (mean diameter) became 19.2 mm (range, 9.8-36.1 mm). The average tumor marginal dose was 12.1Gy (range, from 10-14 Gy). The mean follow-up period was 32 months after radiosurgery.

RESULTS:
The tumor size decreased in 6 patients, unchanged in 5 patients, and increased in 3 patients. Only 1 patient (7%) with extra large tumor needed surgical resection 1 year after radiosurgery. Excellent facial nerve function (House & Brackmann Grade I or II) was preserved in 12 patients (85.7%) in the final follow-up.

CONCLUSIONS:
In the case of large acoustic neuromas, subtotal removal and subsequent radiosurgery is one option for maintaining cranial nerve function and long-term tumor growth control.
**IMPORTANT COMPARISON SURGERY VS GAMMA KNIFE**

**J Neurosurg. 2002 Nov;97(5):1091-100.**

Functional outcome after gamma knife surgery or microsurgery for vestibular schwannomas.

Regis J, Pellet W, Delsanti C, Dufour H, Roche PH, Thomassin JM, Zanaret M, Peragut JC.

Department of Stereotactic and Functional Neurosurgery, Timone Hospital, Marseille, France. jregis@ap-hm.fr

**OBJECT:**

Microsurgical excision is an established treatment for vestibular schwannoma (VS). In 1992 the authors used a patient questionnaire to evaluate the functional outcome and quality of life in a series of 224 consecutive patients. In addition, starting with gamma knife surgery (GKS) in 1992, the authors decided to use the same methodology to evaluate prospectively the results of this modality to compare the two alternatives.

**METHODS:**

Among the 500 patients who were included prospectively, the authors only evaluated patients in whom GKS was the primary treatment for unilateral VS. Four years of follow up was available for the first 104 consecutive patients. Statistical analysis of the GKS and microsurgery populations has shown that only a comparison of Stage II and III (according to the Koos classification) was meaningful in terms of group size and preoperative risk factor distribution. Objective results and questionnaire answers from the first 97 consecutive patients were compared with the 110 patients in the microsurgery group who fulfilled the inclusion criteria. Questionnaire answers indicated that 100% of patients who underwent GKS compared with 63% of patients who underwent microsurgery had no new facial motor disturbance. Forty-nine percent of patients who underwent GKS (17% in the microsurgery study) had no ocular symptoms, and 91% of patients treated with GKS (61% in the microsurgery study) had no functional deterioration after treatment. The mean hospitalization stay was 3 days after GKS and 23 days after microsurgery. All the patients who underwent GKS who had been employed, except one, had kept the same professional activity (56% in the microsurgery study). The mean time away from work was 7 days for GKS (130 days in the microsurgery study). Among patients whose preoperative hearing level was Class 1 according to the Gardner and Robertson scale, 70% preserved functional hearing after GKS (Class 1 or 2) compared with only 37.5% in the microsurgery group.

**CONCLUSIONS:**

Functional side effects happen during the first 2 years after radiosurgery. Findings after 4 years of follow up indicated that GKS provided better functional outcomes than microsurgery in this patient series.
Cranial nerve preservation after radiosurgery of vestibular schwannomas.


Department of Neurosurgery, Karl-Franzens University, Graz, Austria.

Radiosurgery is a management approach used to treat patients with vestibular schwannomas. The goals are long-term tumour growth control, maintenance of cranial nerve function and prevention of new deficiencies. We sought to determine long-term outcomes measuring the potential benefits against the neurological risks of primary radiosurgery. Gamma Knife radiosurgery was applied as a treatment modality for 289 patients with vestibular schwannomas from April 1992 to April 2002. The long-term results of 100 patients who underwent radiosurgery were evaluated. 60 patients received a primary treatment, 40 other cases presented with previously performed subtotal microsurgical resection or recurrence of disease (12-96 months, median 39). The median treatment volume was 3.4 ccm and the median dose to the tumour margin was 13 Gy. The median patient follow-up time was 76 months (range 60-120 months). Four tumours progressed after primary radiosurgery. Tumour control rate was 96%. Useful hearing (Gardner-Robertson I/II) was preserved in 16 patients (55%). Clinical neurological improvement occurred in 50%. Adverse effects comprised neurological symptoms (incomplete facial palsy) (House-Brackman II/III) in six cases (four recovered completely), mild transient trigeminal neuropathy in five cases, and morphological changes displaying rapid enlargement of preexisting macrocysts in two patients and tumour growth in two other patients. Microsurgical resection was performed in four cases (4%) and two patients underwent a shunting procedure because of hydrocephalus formation (2%). In patients who had undergone previous microsurgery, no new cranial nerve deficit was observed. Radiosurgery is an effective method for growth control of vestibular schwannomas and is associated with both a low mortality rate and a good quality of life. Accordingly, for the preservation of cranial nerve function radiosurgery is a useful method for the management of properly selected patients and is comparable to microsurgery.
Gamma surgery for vestibular schwannoma.
Prasad D, Steiner M, Steiner L.

Department of Neurological Surgery, Lars Leksell Center for Gamma Surgery, University of Virginia, Charlottesville, USA. dprasad@virginia.edu

OBJECT
The goal of this study was to assess the results of gamma surgery (GS) for vestibular schwannoma (VS) in 200 cases treated over the last 10 years and to review the role of this neurosurgical procedure in the management of VS.

METHODS
Follow-up reviews ranging from 1 to 10 years were available in 153 of these patients. Follow-up images in these cases were analyzed using computer software that we developed to obtain volume measurements for the tumors, and the clinical condition of the patients was assessed using questionnaires. Gamma surgery was the primary treatment modality in 96 cases and followed microsurgery in 57 cases. Tumors ranged in volume from 0.02 to 18.3 cm$^3$. In the group in which GS was the primary treatment, a decrease in volume was observed in 78 cases (81%), no change in 12 (12%), and an increase in volume in six cases (6%). The decrease was more than 75% in seven cases. In the group treated following microsurgery, a decrease in volume was observed in 37 cases (65%), no change in 14 (25%), and an increase in volume in six (11%). The decrease was more than 75% in eight cases. Five patients experienced trigeminal dysfunction; in three cases this was transient and in the other two it was persistent, although there has been improvement. Three patients had facial paresis (in one case this was transient, lasting 6 weeks; in one case there was 80% recovery at 18 months posttreatment; and in one case surgery was performed after the onset of facial paresis for presumed increase in tumor size). Over a 6-year period, hearing deteriorated in 60% of the patients. Three patients showed an improvement in hearing. No hearing deterioration was observed during the first 2 years of follow-up review. CONCLUSIONS: Gamma surgery should be used to treat postoperative residual tumors as well as tumors in patients with medical conditions that preclude surgery. Microsurgery should be performed whenever a surgeon is confident of extirpating the tumor with a risk-benefit ratio superior to that presented in this study.
5. Pituitary adenomas

Pituitary adenomas are benign tumors of the pituitary gland within the sella in the base of the skull. Sometimes these adenomas present as a slowly growing mass with potential pressure against the optic nerve or chiasm (crossing of optic nerves) without any hormone production. These tumors are called non-secreting pituitary adenoma and are typically removed with open neurosurgery when there is a mass effect. If the neurosurgeon has to leave a tumor rest in order to maintain neurological function, the remaining adenoma can be treated with Gamma Knife radiosurgery in order to prevent later tumor growth.

Other adenomas present as hormone-secreting tumors with an increased production of growth hormone, cortisol or prolactin. Patients with these tumors require immediate relief of their symptoms. Microsurgery is typically used as the first-line treatment. Prolactin-producing tumors are usually treated medically.

When hormone-producing tumors cannot be removed completely or when the tumor recurs after surgery, further treatment is imperative in order to stop excess hormone secretion. Gamma Knife radiosurgery is ideally suited in this situation since the required high-radiation doses can be applied locally with extreme precision, while complex treatment planning protects the visual pathways.

In these cases Gamma Knife radiosurgery has been shown to normalize the excessive hormone production. With Gamma Knife radiosurgery, the elevated hormone levels generally decrease slowly within several months. Due to this known latency period, Gamma Knife radiosurgery is generally not preferred over a surgical resection with immediate effects.

Some of the published results that document this effect in the medical literature are cited in the tables below.

Selected Literature 1998-2012: Gamma Knife Radiosurgery for Pituitary Adenoma (Acromegaly)

**J Neurooncol. 2012 Apr 26. [Epub ahead of print]**

Gamma knife radiosurgery for clinically persistent acromegaly.
Abstract
Gamma knife radiosurgery (GKRS) is an important additional strategy for unresected clinically active pituitary adenomas. Radiosurgery for acromegaly aims to achieve tumor growth control and endocrine remission, potentially obviating the need for lifetime medication suppression therapy. Forty patients with clinically active acromegaly underwent GKRS between 1988 and 2009. Thirty-four patients had undergone prior surgical resection. The median follow-up interval was 72 months (range 24-145). Endocrine remission was defined as growth hormones (GH) level <2.5 ng/ml and a normal insulin-like growth factor 1 (IGF-1) level (age and sex adjusted) off growth hormone inhibiting drugs for at least 3 months. Endocrine control was defined as normal GH and IGF-1 levels on suppression medication. Endocrine remission was achieved in 19 (47.5 %) patients and endocrine control in four additional (10.0 %) patients. Patients with lower IGF-1 level and with tumors that were less invasive of the cavernous sinus before GKRS were associated with better GH remission rates. Imaging-defined local tumor control was achieved in 39 (97.5 %) patients (27 had tumor regression). One patient with delayed tumor progression underwent a second GKRS procedure. Three other patients had repeat GKRS because of persistently elevated and clinically symptomatic GH and IGF-1 levels. Sixteen (40.0 %) patients eventually developed a new pituitary axis deficiency at a median onset of 36 months after radiosurgery. No patient developed new visual dysfunction. Gamma knife radiosurgery, which is most often applied in clinically symptomatic acromegaly persistent after initial microsurgery, was most effective when the tumor was less invasive of the cavernous sinus and when patients had lower IGF-1 levels before GKRS. Almost one half of the patients no longer required long term medication suppression.

IMPORTANT: large series
Results of gamma knife radiosurgery in acromegaly.
Franzin A, Spatola G, Losa M, Picozzi P, Mortini P.

Abstract
Objective. Single-session radiosurgery with Gamma Knife (GK) may be a potential adjuvant treatment in acromegaly. We analyzed the safety and efficacy of GK in patients who had previously received maximal surgical debulking at our hospital.
METHODS
The study was a retrospective analysis of hormonal, radiological, and ophthalmologic data collected in a predefined protocol from 1994 to 2009. The mean age at treatment was 42.3 years (range 22-67 years). 103 acromegalic patients participated in the study. The median follow-up was 71 months (IQ range 43-107). All patients were treated with GK for residual or recurrent GH-secreting adenoma.

RESULTS
Sixty-three patients (61.2%) reached the main outcome of the study. The rate of remission was 58.3% at 5 years (95% CI 47.6-69.0%). Other 15 patients (14.6%) were in remission after GK while on treatment with somatostatin analogues. No serious side effects occurred after GK. Eight patients (7.8%) experienced a new deficit of pituitary function. New cases of hypogonadism, hypothyroidism, and hypoadrenalism occurred in 4 of 77 patients (5.2%), 3 of 95 patients (3.2%), and 6 of 100 patients at risk (6.0%), respectively.

CONCLUSION
In a highly selected group of acromegalic patients, GK treatment had good efficacy and safety.

Gammaknife radiosurgery in patients with acromegaly.
Erdur FM, Kilic T, Peker S, Celik O, Kadioglu P.
Division of Endocrinology and Metabolism, Department of Internal Medicine, Cerrahpasa Medical School, University of Istanbul, Istanbul 34303, Turkey.

Abstract
We aimed to evaluate the efficacy and reliability of gamma-knife radiosurgery (GKR) in 22 patients with acromegaly at the Endocrinology-Metabolism Clinic of Cerrahpasa Medical School. We collected data retrospectively from hospital records on disease activity and other pituitary functions, pituitary MRI and visual fields, before GKR and 6, 12, 24, 36, 48 and 60 months after GKR. The median follow-up duration after GKR was 60 months (interquartile range [IQR]: 24-60 months). The remission rate was 54.5% after the 60 months of follow-up. The median growth hormone (GH) level at 60 months after GKR (0.99 ng/mL [IQR: 0.36-2.2]) was significantly lower than the median GH level before GKR (5.65 ng/mL [IQR: 3.85-7.2] (p=0.002). The median insulin-like growth factor-1 (IGF-1) level 60 months after GKR (221.5 ng/mL [IQR: 149-535]) was significantly lower than the median IGF-1 level before GKR (582.5 ng/mL [IQR: 515-655]) (p=0.008). Tumour growth was well controlled in 20 patients (95.2%). Six patients (28.6%) developed new-onset hypopituitarism. We concluded that GKR is an effective adjuvant treatment to control tumour growth, lower GH and IGF-1 levels, and
to increase remission rates in patients with acromegaly who were refractory to surgical and medical treatment.

J Neurosurg. 2010 Dec;113 Suppl:149-152.
Predictors of outcome following Gamma Knife surgery for acromegaly.
Poon TL, Leung SC, Poon CY, Yu CP.

Department of Neurosurgery, Queen Elizabeth Hospital, Hong Kong SAR, People's Republic of China. poontaklap@yahoo.com.hk

OBJECT
Gamma Knife surgery (GKS) is gaining popularity in the treatment of patients with acromegaly after transsphenoidal tumor excision. In this paper, the authors examine the efficacy of GKS and predictors for biochemical remission.

METHODS
The authors retrospectively reviewed data spanning the period 1997–2008 in their hospital Gamma Knife statistics database. Forty patients with a mean age of 64 years (range 19–73 years) underwent GKS for acromegaly during that period. Transsphenoidal subtotal tumor excision had been performed prior to GKS in all these patients, except for 3 deemed to be at high surgical risk. All GKS treatment plans were formulated by the same team that performed the microsurgical procedures. Biochemical remission was defined as a growth hormone (GH) level <2 ng/ml and an insulin-like growth factor–I level that was considered normal with reference to the patient's age and sex. The mean follow-up period after radiosurgery was 73.8 months (range 12–132 months).

RESULTS
Three patients died during the study period of causes unrelated to surgery or GKS. Twenty-nine patients (72.5%) underwent 1 radiosurgery session, and 11 patients (27.5%) required 2 radiosurgery sessions. Among the patients who underwent 1 radiosurgery session, excellent responses (76%–100% reductions in tumor size, GH level, and insulin-like growth factor–I level) were observed in 18 (62%; p < 0.0001), 20 (69%; p < 0.0001), and 5 patients (17%; p = 0.21), respectively. Tumors < 1 cm3 and those with no evidence of cavernous sinus extension were statistically significantly related to a good response in tumor size reduction (p = 0.029 and p = 0.0016, respectively). Subgroup analyses were performed in patients who attained biochemical remission in GH levels; the subgroups included patient sex, patient age, target volume, isodose volume, prescribed dose and isodose, pre-GKS GH level, and evidence of cavernous sinus extension. Only male sex was found to be a statistically significant predictor of good hormone regulation (p = 0.0124). The presence of a cavernous sinus extension was the statistically significant predictor of poor hormone control (p = 0.0011) in our study.

CONCLUSIONS
Subtotal tumor excision followed by GKS was an effective treatment for acromegaly. Tumors < 1 cm³ and those with no evidence of cavernous sinus extension responded well to treatment. Male sex and absence of cavernous sinus involvement can be regarded as predictors of biochemical remission.

A systematic analysis of disease control in acromegaly treated with radiosurgery.
Yang I, Kim W, De Salles A, Bergsneider M.

Department of Neurological Surgery, University of California, Los Angeles, California 90095-6901, USA. iyang@mednet.ucla.edu

OBJECT
Stereotactic radiosurgery (SRS) has emerged as an adjuvant radiation-based therapy for pituitary adenomas. Here, the authors present a systematic analysis of SRS for growth hormone-secreting adenomas to characterize the efficacy of SRS in the treatment of acromegaly.

METHODS
A comprehensive search of the English language literature revealed 970 patients with new, recurrent, or persistent acromegaly that had been treated using SRS along with assessable and quantifiable outcome data. Articles published between June 1998 and September 2009 were included in the analysis. Patient outcome data were aggregated and investigated based on tumor size, radiosurgery dose, and clinical outcomes both with and without medication.

RESULTS
The overall disease control rate without medication was 48%-53%, and the overall disease control rate with or without medication was 73%. The overall mean duration of the reported follow-up was 48.5 ± 25.8 months. The mean overall tumor volume in this analysis was 2.11 ± 1.16 cm³. The Pearson product-moment correlation coefficient for tumor volume and cure rate was not significant (r = 0.0668, p = 0.8546).

CONCLUSIONS
Data from this analysis suggest that tumor size may not be a significant prognostic factor in disease control after radiosurgery for acromegaly. The overall disease control rate was approximately 48% without suppressive medications after radiosurgery for acromegaly. With the advancement of increasingly sophisticated stereotactic planning and tumor targeting, the precision of radiosurgery may continue to improve in the treatment of acromegaly.
Gamma Knife radiosurgery in pituitary adenomas: Why, who, and how to treat?
Castinetti F, Brue T.

Department of Endocrinology, La Timone Hospital, Marseille, France. castinetti@univmed.fr

Abstract
Pituitary adenomas are benign tumors that can be either secreting (acromegaly, Cushing's disease, prolactinomas) or non-secreting. Transsphenoidal neurosurgery is the gold standard treatment; however, it is not always effective. Gamma Knife radiosurgery is a specific modality of stereotactic radiosurgery, a precise radiation technique. Several studies reported the efficacy and low risk of adverse effects induced by this technique: in secreting pituitary adenomas, hypersecretion is controlled in about 50% of cases and tumor volume is stabilized or decreased in 80-90% of cases, making Gamma Knife a valuable adjunctive or first-line treatment. As hormone levels decrease progressively, the main drawback is the longer time to remission (12-60 months), requiring an additional treatment during this period. Hypopituitarism is the main side effect, observed in 20-40% cases. Gamma Knife is thus useful in the therapeutic algorithms of pituitary adenomas in well-defined indications, mainly low secreting small lesions well identified on magnetic resonance imaging (MRI).

Gamma Knife surgery for pituitary adenomas: factors related to radiological and endocrine outcomes.

Department of Neurological Surgery, University of Virginia Health System, Charlottesville, Virginia 22908, USA. jps2f@virginia.edu

OBJECT
Gamma Knife surgery (GKS) is a common treatment for recurrent or residual pituitary adenomas. This study evaluates a large cohort of patients with a pituitary adenoma to characterize factors related to endocrine remission, control of tumor growth, and development of pituitary deficiency.

METHODS
A total of 418 patients who underwent GKS with a minimum follow-up of 6 months (median 31 months) and for whom there was complete follow-up were evaluated. Statistical analysis was performed to evaluate for significant factors (p < 0.05) related to treatment outcomes.

RESULTS
In patients with a secretory pituitary adenoma, the median time to endocrine remission was 48.9 months. The tumor margin radiation dose was inversely correlated with time to endocrine remission. Smaller adenoma volume correlated with improved endocrine remission in those with secretory adenomas. Cessation of pituitary suppressive medications at the time of GKS had a trend toward statistical significance in regard to influencing endocrine remission. In 90.3% of patients there was tumor control. A higher margin radiation dose significantly affected control of adenoma growth. New onset of a pituitary hormone deficiency following GKS was seen in 24.4% of patients. Treatment with pituitary hormone suppressive medication at the time of GKS, a prior craniotomy, and larger adenoma volume at the time of radiosurgery were significantly related to loss of pituitary function.

CONCLUSIONS
Smaller adenoma volume improves the probability of endocrine remission and lowers the risk of new pituitary hormone deficiency with GKS. A higher margin dose offers a greater chance of endocrine remission and control of tumor growth.

Gamma knife radiosurgery: a safe and effective salvage treatment for pituitary tumours not controlled despite conventional radiotherapy.
Swords FM, Monson JP, Besser GM, Chew SL, Drake WM, Grossman AB, Plowman PN.
Department of Oncology, Barts and the London NHS Trust, West Smithfield, London EC1A 7BE, UK.

Abstract
OBJECTIVE
We report the use of 'gamma knife' (GK) radiosurgery in 25 patients with pituitary adenomas not cured despite conventional therapy, including external beam radiotherapy.

PATIENTS AND METHODS
All patients had previously received conventional radiotherapy for a mean of 11.8 years prior to receiving GK; 23 out of 25 had also undergone pituitary surgery on at least one occasion. Seventeen had hyperfunctioning adenomas that still required medical therapy without an adequate biochemical control—ten somatotroph adenomas, six corticotroph adenomas and one prolactinoma, while eight patients had non-functioning pituitary adenomas (NFPAs).

RESULTS
Following GK, mean GH fell by 49% at 1 year in patients with somatotroph tumours. Serum IGF1 fell by 32% at 1 year and by 38% at 2 years. To date, 80% of the patients with acromegaly have achieved normalisation of IGF1, and 30% have also achieved a mean GH level of <1.8 ng/ml correlating with normalised mortality. A total of 75% NFPAs showed
disease stabilisation or shrinkage post GK. The patient with a prolactinoma showed a dramatic response: 75% reduction in prolactin at 2 years, with a marked shrinkage on magnetic resonance imaging. The results in corticotroph adenomas were variable. Prior to GK, 72% of the patients were panhypopituitary, and 42% of the remainder have developed new anterior pituitary hormone deficiencies to date. No other adverse events have been detected at a mean follow-up of 36.4 months.

**CONCLUSIONS**
These data indicate that GK is a safe and effective adjunctive treatment for patients with NFPAs and acromegaly not satisfactorily controlled with surgery and radiotherapy.

Efficacy and tolerability of gamma knife radiosurgery in acromegaly: a 10-year follow-up study.

Department of Medical Sciences, University of Milan, Milan Unit of Endocrinology and Diabetology, Fondazione Ospedale Maggiore IRCCS, Milan, Italy. cristina.ronchi@unimi.it

**OBJECTIVE**
The long-term efficacy and safety of stereotactic radiosurgery by gamma knife (GK) still remain unknown. The aim of the study was to investigate the long-term efficacy and tolerability of GK in acromegalic patients.

**DESIGN AND PATIENTS**
Retrospective analysis for a median follow-up of 10 years. Thirty-five acromegalic patients from two referral centres in Milan submitted to GK (median margin dose: 20 Gy, median % isodose: 50) between 1995 and 2004.

**MAIN OUTCOME MEASURES**
GH/IGF-I secretion, anterior pituitary function, radiological imaging and ophthalmological data.

**RESULTS**
**Cure rate improved over time (up to 46% at 10 years),** as did the proportion of patients achieving control on somatostatin analogues (from 12.5% at baseline to 50% at 10 years). **Normal IGF-I values were observed in 82% of patients at their last visit. No visual impairment, disease recurrence, tumour growth or secondary cerebral tumour occurred.** Half of the patients developed one or more new deficiencies, while two patients normalized their prior failures. In particular, new onset of clinical or **subclinical hypoadrenalism occurred in 12/30 patients (40%), hypothyroidism in 3/28 (11%), hypogonadism in 2/15 (13%) and GH deficiency in 3/25 (12%) patients.**
2/35 (6%). GH value at the time of GK was the best negative predictor of cure and margin dose was the best positive predictor of new hypopituitarism.

CONCLUSIONS
Over a 10-year period after GK radiosurgery, an increasing percentage of patients achieve cure, or adequate control of the disease on pharmacological therapy, at the expense of increasing novel pituitary deficiencies.

Stereotactic radiosurgery for pituitary adenomas: a comprehensive review of indications, techniques and long-term results using the Gamma Knife.
Jagannathan J, Yen CP, Pouratian N, Laws ER, Sheehan JP.

Department of Neurological Surgery, University of Virginia Health Sciences Center, Box 800212, Charlottesville, VA 22908, USA. jj5a@virginia.edu

OBJECT
This study reviews the long-term clinical results of stereotactic radiosurgery in the treatment of pituitary adenoma patients.

METHODS
We reviewed the outcomes of 298 patients who underwent Gamma Knife radiosurgery for recurrent or residual pituitary adenomas. These results are compared to other contemporary radiosurgical series.

RESULTS
Pituitary tumors are well-suited for radiosurgery, since radiation can be focused on a well circumscribed region, while adjacent neural structures in the suprasellar and parasellar regions are spared. The overall rate of volume reduction following stereotactic radiosurgery is 85% for non-secretory adenomas that are followed for more than 1-year. The rates of hormonal normalization in patients with hypersecretory adenomas can vary considerably, and tends to be higher in patients with Cushing's Disease and acromegaly (remission rate of approximately 53% and 54%, respectively) when compared with patients who have prolactinomas (24% remission) and Nelson's syndrome (29%) remission. Advances in dose delivery and modulation of adenoma cells at the time of radiosurgery may further improve results.

CONCLUSIONS
Although the effectiveness of radiosurgery varies considerably depending on the adenoma histopathology, volume, and radiation dose, most studies indicate that radiosurgery when combined with microsurgery is effective in controlling pituitary adenoma growth and hormone hypersecretion. Long-term follow-up is essential to determine the rate of endocrinopathy, visual dysfunction, hormonal recurrence, and adenoma volume control.

**Prog Neurol Surg. 2009;22:77-95.**

Long-term results of stereotactic gamma knife radiosurgery for pituitary adenomas. Specific strategies for different types of adenoma.

Kobayashi T.

Long-term results of gamma knife radiosurgery for pituitary adenomas are presented and treatment strategies for different adenoma types are discussed. _Two hundred and sixty-seven patients with pituitary adenoma have been treated by gamma knife radiosurgery during the past 12 years._ There were 131 cases of nonfunctioning and _136 cases of functioning adenomas_, in which 71 GH-producing, 33 PRL-producing and 32 ACTH-producing adenomas were included. Retreatment with the gamma knife was done in 8 cases because of large tumors or uncontrolled hormones. Micro- and small adenomas could be cured by gamma knife radiosurgery alone. Surgical or chemical debulking was necessary before radiosurgery for a large tumor with extrasellar extension. Retreatment was effective and safe in some cases. Nonfunctioning adenomas showed higher control rates than functioning adenomas even with lower dose treatment. _Cushing disease showed the best response because of the smallest tumor size with the highest dose treatment._ Acromegaly and prolactinoma were difficult to control because of larger tumors with lower dose treatment. The rate of hormone normalization was also high in Cushing disease but lower in prolactinoma and lowest in acromegaly. High-dose treatment was necessary for functioning adenomas to control tumor growth and oversecretion of hormones. In conclusion, gamma knife radiosurgery was effective and safe for the treatment of pituitary adenomas. However, the treatment strategies should be specific to each adenoma type according to the radiosensitivity, chemosensitivity and biological nature of the tumor.

**Neurosurgery. 2008 Jun;62(6):1262-9; discussion 1269-70.**

Gamma knife radiosurgery for acromegaly: outcomes after failed transsphenoidal surgery.


Lars Leksell Gamma Knife Center, Department of Neurosurgery, University of Virginia Health Sciences Center, Charlottesville, Virginia, USA.

**OBJECTIVE**
This study evaluates the safety and efficacy of gamma knife radiosurgery (GKRS) in patients with a growth hormone-secreting adenoma.

**METHODS**
A retrospective review of data collected from a prospective database of GKRS patients between January 1988 and September 2006 was performed in patients with acromegaly. Successful endocrine outcome was defined as normalization of the insulin-like growth factor level. Tumor volume was also assessed. **At least 18 months of follow-up was available in 95 patients** who received radiosurgery during the study period. Mean endocrine follow-up was 57 months (range, 18-168 mo).

**RESULTS**
Normal insulin-like growth factor levels were achieved in 50 patients (53%) at an average time of 29.8 months after radiosurgery (median, 23.5 mo). A decrease in tumor volume control was achieved in 83 (92%) of 90 patients. Five patients (6%) had no change in tumor volume, and two patients (2%) had an increase in tumor volume. **New endocrine deficiencies developed in 32 patients (34%).** Four patients developed new-onset partial visual acuity deficits; three of these patients had received previous conventional fractionated radiation therapy.

**CONCLUSION**
GKRS is a complementary treatment for recurrent or residual growth hormone-secreting pituitary adenomas. Although infrequent, tumor growth, new-onset pituitary hormone deficiency, recurrence, and neurological dysfunction require careful clinical, radiological, and endocrinological follow-up.


Focal radiation therapy for patients with persistent/recurrent pituitary adenoma, despite previous radiotherapy.

Edwards AA, Swords FM, Plowman PN.

Department of Radiotherapy, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE, UK.

With the stricter endocrine definitions of cure following conventionally planned and fractionated radiotherapy for functioning pituitary adenomas, together with the move in the profession (since the advent of high quality MRI) to postpone radiation therapy until macroscopic disease appears after surgery, **it is now realised that cure rates following conventional radiotherapy approximate three out of four rather than the >90% cited for more than a decade.** Patients with persistent active tumours may be successfully further treated by focal radiation therapy by one of the stereotactic focal techniques. We have experience of such re-treatment radiation therapy in 50 patients. **With careful case selection, we here demonstrate that in acromegaly, for example, normalisation of both GH and IGF levels may be achieved in 37-58% of these previously irradiated**
patients with low risk of late morbidity. Unquestionably, growth delay occurs in many cases but the long term tumour control rate has yet to be established.

Surgery for acromegaly: evolution of the techniques and outcomes.
Laws ER.

Department of Neurosurgery, Stanford University Medical Center, 300 Pasteur Drive, Stanford, CA 94305, USA. erlaws@stanford.edu

This paper presents an overview of the evolution of pituitary surgery for acromegaly. It begins with the first case, attempted in 1893, through the initial transsphenoidal successes in 1907-1910, to the development of effective craniotomy approaches, and ultimately to the resurrection of the transsphenoidal approach in the 1970s and thereafter. Today, the minimally endoscopic transnasal endoscopic approach is fast becoming the norm. Indications for surgery include active acromegaly, visual loss and other forms of mass effect, pituitary tumor apoplexy, and failure of other therapies (medical, radiation). Contraindications include advanced age, debility or other medical conditions increasing the risk of general anaesthesia or surgery. **Surgery for acromegaly has the advantage of immediate lowering of the growth hormone excess, with endocrine remission rates of 70% for microadenomas and 50% for macroadenomas.** When surgery fails to obtain remission, a program of therapy is designed for the patient to include adjunctive medical therapy (dopamine agonists, somatostatin analogs, and growth hormone receptor antagonists), radiation therapy or radiosurgery (Gamma knife, Cyberknife, etc.).

**Eur J Endocrinol. 2007 Sep;157(3):255-63.**
Gamma knife stereotactic radiosurgery for acromegaly.

Department of Neurosurgery, Haukeland University Hospital, Bergen, Norway. e.o.vik-mo@medisin.uio.no

**BACKGROUND**
Gamma knife radiosurgery (GKR) is an adjuvant treatment for acromegaly if surgery fails to normalize GH hypersecretion.

**OBJECTIVE:**
To examine the effect of GKR on tumor growth and hypersecretion, and to characterize the adverse effect of this treatment.

**DESIGN:**
Cross-sectional follow-up study. First, retrospective data pre- and post-GKR were collected. Patients then underwent a predefined survey including radiological, endocrinological, ophthalmological, and neurosurgical evaluation. Setting: Norwegian National Center for gamma knife treatment. Patients: **Sixty-one patients treated with GKR for acromegaly.** Out of 55, 53 living patients underwent a detailed survey. The **mean follow-up was 5.5 years.** No patient was lost to follow-up.

**RESULTS:**
Tumor growth was stopped in all patients. At 3, 5, and 10 years after GKR, 45, 58, and 86% of patients had normal IGF-I levels. Consecutive hormone value analysis showed that patients receiving GH-suppressive medication had a more rapid decline in hypersecretion than those who did not receive such medication. Evaluated by survey baseline values alone, non-elevated IGF-I and GH levels below 5 mIU/l were found in 38%. **GH-suppressive medication was terminated in 16 out of 40 patients following GKR.** Nine out of 53 surveyed patients (17%) had normal IGF-I and GH nadir below 2.6 mIU/l at glucose tolerance tests, while not on hormone-suppressive medication. Two patients developed minor visual field defects. Eight patients started hormone substitution therapy during the follow-up period.

**CONCLUSION:**
GKR is an effective adjuvant treatment for residual acromegaly, carrying few side effects.

*J Neurosurg. 2007 May;106(5):833-8.*
Radiosurgery of growth hormone-producing pituitary adenomas: factors associated with biochemical remission.
Pollock BE, Jacob JT, Brown PD, Nippoldt TB.

Department of Neurological Surgery, Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Mayo Clinic College of Medicine, Rochester, Minnesota 55905, USA.

**OBJECT**
The authors reviewed outcomes after stereotactic radiosurgery for patients with acromegaly and analyzed factors associated with biochemical remission.

**METHODS:**
Retrospective analysis was performed for **46 consecutive cases of growth hormone (GH)-producing pituitary adenomas treated by radiosurgery between 1991 and 2004.** Biochemical remission was defined as a fasting GH less than 2 ng/ml and a normal age- and sex-adjusted insulin-like
growth factor-I (IGF-I) level while patients were not receiving any pituitary suppressive medications. The median follow up after radiosurgery was 63 months (range 22-168 months). Twenty-three patients (50%) had biochemical remission documented at a median of 36 months (range 6-63 months) after one radiosurgical procedure. The actuarial rates of biochemical remission at 2 and 5 years after radiosurgery were 11 and 60%, respectively. Multivariate analysis showed that IGF-I levels less than 2.25 times the upper limit of normal (hazard ratio [HR] 2.9, 95% confidence interval [CI] 1.2-6.9, p = 0.02) and the absence of pituitary suppressive medications at the time of radiosurgery (HR 4.2, 95% CI 1.4-13.2, p = 0.01) correlated with biochemical remission. The incidence of new anterior pituitary deficits was 10% at 2 years and 33% at 5 years.

CONCLUSIONS:
Discontinuation of pituitary suppressive medications at least 1 month before radiosurgery significantly improved endocrine outcomes for patients with acromegaly. Patients with GH-producing pituitary adenomas should not undergo further radiation therapy or surgery for at least 5 years after radiosurgery because GH and IGF-I levels continue to normalize over that interval.

Clin Endocrinol (Oxf). 2006 May;64(5):588-95.
Gamma knife radiosurgery for acromegaly--long-term experience.

Third Department of Medicine, First Medical Faculty, Charles University, Prague, Czech Republic.

OBJECTIVE
The Leksell gamma knife (LGK) is one of the treatment options for pituitary adenomas. We report on our long-term experience treating acromegaly using LGK. DESIGN: Since 1993 we have followed 96 acromegaly patients through periods of from 12 to 120 months. The mean follow-up period was 53.7 +/- 26.8 months. Seventy-two patients were treated with neurosurgery prior to LGK; for 24 LGK was the primary treatment. Thirteen patients were irradiated twice, due to persistent activity of the adenoma or its residue. Pituitary functions were tested at 6-month intervals, post-irradiation. The target tumour volume for radiosurgery was between 93.3 and 12 700 mm3 (median 1350 mm3).

RESULTS:
Fifty per cent of the patients achieved mean GH < 2.5 microg/l within 42 months, normalized their IGF-I within 54 months, and achieved GH suppression in the oral glucose tolerance test (oGTT) < 1 microg/l with normal IGF-I within 66 months. LGK effectiveness was dependent on initial adenoma hormonal activity (GH and IGF-I serum levels), not on the size of the adenoma. Patients with primary neurosurgery followed by LGK irradiation had better outcomes than those with LGK alone. Irradiation arrested all adenoma growth, causing tumour shrinkage in 62.3% of
patients. **Twenty-six developed hypopituitarism when irradiated by 15 Gy (or more) on functional peritumoral pituitary tissue.** No hypopituitarism appeared using lower doses.

**CONCLUSIONS:**
In acromegaly, LGK is a useful adjunct to primary neurosurgery when treating post-surgical residues because it can limit the duration of medical therapy. It can be used as a primary therapy when neurosurgery is not possible.

Outcome of gamma knife radiosurgery in 82 patients with acromegaly: correlation with initial hypersecretion.
Castinetti F, Taieb D, Kuhn JM, Chanson P, Tamura M, Jaquet P, Conte-Devolx B, Régis J, Dufour H, Brue T.

Federation of Endocrinology, Diabetes, Metabolic Diseases and Nutrition, Hôpital de la Timone, Centre Hospitalier Universitaire de Marseille and Faculté de Médecine, Université de la Méditerranée, Marseille, France.

**CONTEXT**
Because surgical and medical therapies of acromegaly all have specific limitations, radiotherapy has been used as an adjunctive strategy. Stereotactic radiosurgery has not yet been widely evaluated.

**OBJECTIVE:**
The objective was to perform an analysis of long-term hormonal effects and tolerance of gamma knife radiosurgery.

**DESIGN:**
Eighty-two patients were prospectively studied over a decade, with a mean follow-up of 49.5 months.

**SETTING:**
All patients were treated at the Department of Functional Neurosurgery of Marseille, France. PATIENTS: The patients included 82 with active acromegaly, of whom 63 had previous transsphenoidal surgery.

**INTERVENTION:**
Intervention included radiosurgery using the Leksell Gamma Unit B model.

**MAIN OUTCOME MEASURES:**
Remission was diagnosed when mean GH levels were less than 2 ng/ml and IGF-I was normal for age off somatostatin agonists (at least 3 months).

**RESULTS:**
Seventeen percent of the patients were in remission without any treatment. Twenty-three percent previously uncontrolled on somatostatin agonists fulfilled the same criteria after gamma knife while
maintained on medical treatment. Initial GH and IGF-I levels off somatostatin agonists were significantly higher in uncured than in remission group (P = 0.01 and 0.047, respectively). Withdrawal of somatostatin agonists at the time of radiosurgery had no incidence on the outcome. No significant difference was found in success rate whether patients had previously been treated or not. Long-term side effects included complete (n = 2) or partial (n = 12) hypopituitarism diagnosed 1-7 yr after gamma knife.

CONCLUSIONS:
Gamma knife radiosurgery may represent a therapeutic approach in patients with moderate initial or residual GH hypersecretion.

Low Dose!

**J Neurosurg. 2005 Jan;102 Suppl:119-23.**

Long-term results of gamma knife surgery for growth hormone-producing pituitary adenoma: is the disease difficult to cure?
Kobayashi T, Mori Y, Uchiyama Y, Kida Y, Fujitani S.

Radiosurgery Center, Nagoya Kyoritsu Hospital and Gamma Knife Center, Komaki City Hospital, Nagoya, Japan.

**OBJECT**
The authors conducted a study to determine the long-term results of gamma knife surgery for residual or recurrent growth hormone (GH)-producing pituitary adenomas and to compare the results with those after treatment of other pituitary adenomas.

**METHODS**
The series consisted of **67 patients**. The mean tumor diameter was 19.2 mm and volume was 5.4 cm3. The mean maximum dose was 35.3 Gy and the **mean margin dose was 18.9 Gy**. The **mean follow-up duration was 63.3 months** (range 13-142 months). The tumor resolution rate was 2%, the response rate 68.3%, and the control rate 100%. **Growth hormone normalization (GH < 1.0 ng/ml) was found in 4.8%, nearly normal (< 2.0 ng/ml) in 11.9%, significantly decreased (< 5.0 ng/ml) in 23.8%, decreased in 21.4%, unchanged in 21.4%, and increased in 16.7%. Serum insulin-like growth factor (IGF)-1 was significantly decreased (IGF-1 < 400 ng/ml) in 40.7%, decreased in 29.6%, unchanged in 18.5%, and increased in 11.1%, which was almost parallel to the GH changes.**

**CONCLUSIONS**
Gamma knife surgery was effective and safe for the control of tumors; however, normalization of GH and IGF-1 secretion was difficult to achieve in cases with large tumors and low-dose radiation. Gamma knife radiosurgery is thus indicated for small tumors after surgery or medication therapy when a relatively high-dose radiation is required.
Gamma-knife radiosurgery in acromegaly: a 4-year follow-up study.

Division of Endocrinology, Ospedale Niguarda, Milan, Italy.

Stereotactic radiosurgery by gamma-knife (GK) is an attractive therapeutic option after failure of microsurgical removal in patients with pituitary adenoma. In these tumors or remnants of them, it aims to obtain the arrest of cell proliferation and hormone hypersecretion using a single precise high dose of ionizing radiation, sparing surrounding structures. The long-term efficacy and toxicity of GK in acromegaly are only partially known. Thirty acromegalic patients (14 women and 16 men) entered a prospective study of GK treatment. Most were surgical failures, whereas in 3 GK was the primary treatment. Imaging of the adenoma and target coordinates identification were obtained by high resolution magnetic resonance imaging. All patients were treated with multiple isocenters (mean, 8; range, 3-11). The 50% isodose was used in 27 patients (90%). The mean margin dose was 20 Gy (range, 15-35), and the dose to the visual pathways was always less than 8 Gy. After a median follow-up of 46 months (range, 9-96), IGF-I fell from 805 micro g/liter (median; interquartile range, 640-994) to 460 micro g/liter (interquartile range, 217-654; P = 0.0002), and normal age-matched IGF-I levels were reached in 7 patients (23%). Mean GH levels decreased from 10 micro g/liter (interquartile range, 6.4-15) to 2.9 micro g/liter (interquartile range, 2-5.3; P < 0.0001), reaching levels below 2.5 micro g/liter in 11 (37%). The rate of persistently pathological hormonal levels was still 70% at 5 yr by Kaplan-Meier analysis. The median volume was 1.43 ml (range, 0.20-3.7). Tumor shrinkage (at least 25% of basal volume) occurred after 24 months (range, 12-36) in 11 of 19 patients (58% of assessable patients). The rate of shrinkage was 79% at 4 yr. In no case was further growth observed. Only 1 patient complained of side-effects (severe headache and nausea immediately after the procedure, with full recovery in a few days with steroid therapy). Anterior pituitary failures were observed in 2 patients, who already had partial hypopituitarism, after 2 and 6 yr, respectively. No patient developed visual deficits. GK is a valid adjunctive tool in the management of acromegaly that controls GH/IGF-I hypersecretion and tumor growth, with shrinkage of adenoma and no recurrence of the disease in the considered observation period and with low acute and chronic toxicity.
**Clin Endocrinol (Oxf). 2006 May;64(5):588-95.**

Gamma knife radiosurgery for acromegaly--long-term experience.


Third Department of Medicine, First Medical Faculty, Charles University, Prague, Czech Republic.

**fjjezek@cmail.cz**

**OBJECTIVE**

The Leksell gamma knife (LGK) is one of the treatment options for pituitary adenomas. We report on our long-term experience treating acromegaly using LGK. **DESIGN:** Since 1993 we have followed 96 acromegaly patients through periods of from 12 to 120 months. The mean follow-up period was 53.7 +/- 26.8 months. Seventy-two patients were treated with neurosurgery prior to LGK; for 24 LGK was the primary treatment. Thirteen patients were irradiated twice, due to persistent activity of the adenoma or its residue. Pituitary functions were tested at 6-month intervals, post-irradiation. The target tumour volume for radiosurgery was between 93.3 and 12 700 mm³ (median 1350 mm³).

**RESULTS**

Fifty per cent of the patients achieved mean GH < 2.5 microg/l within 42 months, normalized their IGF-I within 54 months, and achieved GH suppression in the oral glucose tolerance test (oGTT) < 1 microg/l with normal IGF-I within 66 months. LGK effectiveness was dependent on initial adenoma hormonal activity (GH and IGF-I serum levels), not on the size of the adenoma. Patients with primary neurosurgery followed by LGK irradiation had better outcomes than those with LGK alone. Irradiation arrested all adenoma growth, causing tumour shrinkage in 62.3% of patients. Twenty-six developed hypopituitarism when irradiated by 15 Gy (or more) on functional peritumoral pituitary tissue. No hypopituitarism appeared using lower doses.

**CONCLUSIONS**

In acromegaly, LGK is a useful adjunct to primary neurosurgery when treating post-surgical residues because it can limit the duration of medical therapy. It can be used as a primary therapy when neurosurgery is not possible.
Outcome of gamma knife radiosurgery in 82 patients with acromegaly: correlation with initial hypersecretion.

Castinetti F, Taieb D, Kuhn JM, Chanson P, Tamura M, Jaquet P, Conte-Devolx B, Régis J, Dufour H, Brue T.

Federation of Endocrinology, Diabetes, Metabolic Diseases and Nutrition, Hôpital de la Timone, Centre Hospitalier Universitaire de Marseille and Faculté de Médecine, Université de la Méditerranée, Marseille, France.

CONTEXT
Because surgical and medical therapies of acromegaly all have specific limitations, radiotherapy has been used as an adjunctive strategy. Stereotactic radiosurgery has not yet been widely evaluated.

OBJECTIVE:
The objective was to perform an analysis of long-term hormonal effects and tolerance of gamma knife radiosurgery.

DESIGN:
Eighty-two patients were prospectively studied over a decade, with a mean follow-up of 49.5 months.

SETTING:
All patients were treated at the Department of Functional Neurosurgery of Marseille, France.

PATIENTS:
The patients included 82 with active acromegaly, of whom 63 had previous transsphenoidal surgery.

INTERVENTION:
Intervention included radiosurgery using the Leksell Gamma Unit B model.

MAIN OUTCOME MEASURES:
Remission was diagnosed when mean GH levels were less than 2 ng/ml and IGF-I was normal for age off somatostatin agonists (at least 3 months).

RESULTS:
Seventeen percent of the patients were in remission without any treatment. Twenty-three percent previously uncontrolled on somatostatin agonists fulfilled the same criteria after gamma knife while maintained on medical treatment. Initial GH and IGF-I levels off somatostatin agonists were significantly higher in uncured than in remission group (P = 0.01 and 0.047, respectively). Withdrawal of somatostatin agonists at the time of radiosurgery had no incidence on the
outcome. No significant difference was found in success rate whether patients had previously been treated or not. Long-term side effects included complete (n = 2) or partial (n = 12) hypopituitarism diagnosed 1-7 yr after gamma knife.

CONCLUSIONS
Gamma knife radiosurgery may represent a therapeutic approach in patients with moderate initial or residual GH hypersecretion.

**Pituitary. 1999 Jun;2(1):71-7.**
Role of gamma knife radiosurgery in acromegaly.
Jackson IM, Noren G.

Department of Medicine, Rhode Island Hospital, Providence 02903, USA.

Stereotactic radiosurgery with the Gamma Knife allows the delivery of focused radiation in a single session from a Cobalt-60 source to a pituitary tumor with little radiation to surrounding normal brain tissue. At this time the major role for Gamma Knife radiosurgery in acromegaly is for the treatment of failed pituitary surgery although it may also be used as primary treatment for patients unwilling or unsuitable, for medical reasons, to undergo transsphenoidal surgery. The major risk from Gamma Knife radiosurgery appears to be radiation damage to the visual pathways, but this can be obviated by limiting the radiation dose to the optic chiasm under 10 Gy. In contrast, the neuronal and vascular structures running in the cavernous sinus are much less radiosensitive allowing an ablative dose to be administered to tumors showing lateral invasion and impinging on cranial nerves III, IV, V and VI. Gamma Knife radiosurgery appears to produce effects in GH secreting tumors faster than with fractionated radiotherapy without the potential long-term risk of developing a second extrapituitary brain tumor as well as the neuropsychiatric effects associated with conventional radiation administration.

Stereotactic radiosurgery for recurrent surgically treated acromegaly: comparison with fractionated radiotherapy.

Neurosurgery Department, Institute of Neuroradiology, Klinik Im Park, Zürich, Switzerland.
1000123.1666@compuserve.com

**OBJECT**
The authors tested the assumption that gamma knife radiosurgery is more effective than fractionated radiotherapy for the treatment of patients with acromegaly who have undergone unsuccessful resective surgery. Untreated and uncured acromegaly causes illness and death. Acromegalic patients in whom
growth hormone and, particularly, insulin-like growth factor I are not normalized must undergo further treatment.

METHODS:
After unsuccessful operations, 16 patients suffering from recurrent and uncured acromegaly underwent stereotactic radiosurgery (25 Gy to the tumor margin, 50 Gy maximum), the outcome of which was compared with the result obtained in 50 patients who received fractionated radiotherapy (40 Gy). The cumulative distribution functions of the two groups (Kaplan-Meier estimate) differed significantly (p < 0.0001 in the log-rank test of Mantel). The mean time to simultaneous normalization of both parameters was 1.4 years in the group treated with the gamma knife and 7.1 years in the group treated with fractionated radiotherapy.

CONCLUSIONS:
The authors suggest the use of stereotactic radiosurgery as the preferred treatment for recurrent acromegaly resulting from unsuccessfully resected tumors.

Selected Literature 2000-2010: Gamma Knife Radiosurgery for Pituitary Adenoma (Cushing's disease)

*Curr Opin Endocrinol Diabetes Obes. 2010 Aug;17(4):356-64.*
Starke RM, Williams BJ, Vance ML, Sheehan JP.

Department of Neurological Surgery, University of Virginia, Charlottesville, Virginia 22908, USA.

PURPOSE OF REVIEW
The indications, efficacy, and safety of radiation therapy and stereotactic radiosurgery for Cushing's disease are evaluated. We queried PubMed using the terms, 'Cushing's disease', 'radiotherapy', and 'radiosurgery', then evaluated each study for the number of patients, method of radiation delivery, type of radiation therapy or radiosurgical device used, treatment parameters (e.g. maximal dose, tumor margin dose), length of follow-up, tumor-control rate, complications, rate of hormone normalization, newly onset loss of pituitary function, and method used to assess endocrine remission.

RECENT FINDINGS
A total of 39 peer-reviewed studies with 731 patients were included. The reported rates of tumor-volume control following radiotherapy and radiosurgery vary considerably from 66-100%. Additionally, the reported rates of endocrine remission vary substantially from 17-100%. The
incidence of serious complications following radiosurgery is quite low. Although post-treatment hypopituitarism and disease recurrence were uncommon, they did occur, and this underscores the necessity for long-term follow-up in these patients.

**SUMMARY**
Radiosurgery and, in the modern era, less commonly, radiation therapy, offer both well tolerated and reasonably effective treatment for recurrent or residual Cushing's adenomas.

**J Clin Endocrinol Metab. 2009 Sep;94(9):3400-7. Epub 2009 Jun 9.**
Long-term results of stereotactic radiosurgery in secretory pituitary adenomas.

Service d'Endocrinologie, Diabète, et Maladies Métaboliques, et Centre de Reference des Maladies Rares d'Origine Hypophysaires, Hôpital de la Timone, F-13385 Marseille, France.

**CONTEXT**
To date, no study reported long-term follow-up results of gamma knife stereotactic radiosurgery (SR).

**OBJECTIVE**
The aim of the study was to determine long-term efficacy and adverse effects of SR in secreting pituitary adenomas.

**DESIGN**
We conducted a retrospective study of patients treated by SR in the center of Marseille, France, with a follow-up of at least 60 months.

**PATIENTS**
A total of **76 patients were treated by SR for acromegaly (n = 43), Cushing's disease (CD; n = 18),** or prolactinoma (n = 15) as a primary (n = 27) or adjunctive postsurgical treatment (n = 49).

**MAIN OUTCOME MEASURES**
After withdrawal of antisecretory drugs, patients were considered in remission if they had mean GH levels below 2 ng/ml and normal IGF-1 (acromegaly), normal 24-h urinary free cortisol, and cortisol less than 50 nmol/liter after low-dose dexamethasone test (CD) or two consecutive normal samplings of prolactin levels (prolactinoma).

**RESULTS**
After a mean follow-up of 96 months, **44.7% of the patients were in remission. Mean time to remission was 42.6 months.** Twelve patients presented late remission at least 48 months after SR. Two patients with CD presented late recurrence 72 and 96 months after SR. Forty percent of
patients treated primarily with SR were in remission. Target volume and initial hormone levels were significant predictive factors of remission in univariate analysis. Radiation-induced hypopituitarism was observed in 23% patients; in half of them, hypopituitarism was observed after a mean time of 48 to 96 months. Twenty-four patients were followed for more than 120 months; rates of remission and hypopituitarism were similar to the whole cohort.

CONCLUSIONS
SR is an effective and safe primary or adjunctive treatment in selected patients with secreting pituitary adenomas.

Long-term results of stereotactic gamma knife radiosurgery for pituitary adenomas. Specific strategies for different types of adenoma.
Kobayashi T.
Nagoya Radiosurgery Center, Nagoya Kyoritsu Hospital, Nagoya, Aichi, Japan.

Abstract
Long-term results of gamma knife radiosurgery for pituitary adenomas are presented and treatment strategies for different adenoma types are discussed. Two hundred and sixty-seven patients with pituitary adenoma have been treated by gamma knife radiosurgery during the past 12 years. There were 131 cases of nonfunctioning and 136 cases of functioning adenomas, in which 71 GH-producing, 33 PRL-producing and 32 ACTH-producing adenomas were included. Retreatment with the gamma knife was done in 8 cases because of large tumors or uncontrolled hormones. Micro- and small adenomas could be cured by gamma knife radiosurgery alone. Surgical or chemical debulking was necessary before radiosurgery for a large tumor with extrasellar extension. Retreatment was effective and safe in some cases. Nonfunctioning adenomas showed higher control rates than functioning adenomas even with lower dose treatment. Cushing disease showed the best response because of the smallest tumor size with the highest dose treatment. Acromegaly and prolactinoma were difficult to control because of larger tumors with lower dose treatment. The rate of hormone normalization was also high in Cushing disease but lower in prolactinoma and lowest in acromegaly. High-dose treatment was necessary for functioning adenomas to control tumor growth and oversecretion of hormones. In conclusion, gamma knife radiosurgery was effective and safe for the treatment of pituitary adenomas. However, the treatment strategies should be specific to each adenoma type according to the radiosensitivity, chemosensitivity and biological nature of the tumor.
Gamma Knife surgery for Cushing's disease.

Jagannathan J, Sheehan JP, Pouratian N, Laws ER, Steiner L, Vance ML.

Department of Neurological Surgery, University of Virginia Health System, Charlottesville, Virginia 22908-00212, USA.

OBJECT
In this study the authors address the efficacy and safety of Gamma Knife surgery (GKS) in patients with adrenocorticotropic hormone-secreting pituitary adenomas.

METHODS
A review of data collected from a prospective GKS database between January 1990 and March 2005 was performed in patients with Cushing's disease. All but one patient underwent resection for a pituitary tumor, without achieving remission. Successful endocrine outcome after GKS was defined as a normal 24-hour urinary free cortisol (UFC) concentration posttreatment after a minimum of 1 year of follow up. Patient records were also evaluated for changes in tumor volume, development of new hormone deficiencies, visual acuity, cranial nerve neuropathies, and radiation-induced imaging changes. Ninety evaluable patients had undergone GKS, with a mean endocrine follow-up duration of 45 months (range 12-132 months). The mean dose, to the tumor margin was 23 Gy (median 25 Gy). Normal 24-hour UFC levels were achieved in 49 patients (54%), with an average time of 13 months after treatment (range 2-67 months). In the 49 patients in whom a tumor was visible on the planning magnetic resonance (MR) image, a decrease in tumor size occurred in 39 (80%), in seven patients there was to change in size, and tumor growth occurred in three patients. Ten patients (20%) experienced a relapse of Cushing's disease after initial remission; the mean time to recurrence was 27 months (range 6-60 months). Seven of these patients underwent repeated GKS, with three patients achieving a second remission. New hormone deficiencies developed in 20 patients (22%), with hypothyroidism being the most common endocrinopathy after GKS. Five patients experienced new visual deficits or third, fourth, or sixth cranial nerve deficits; two of these patients had undergone prior conventional fractionated radiation therapy, and four of them had received previous GKS. Radiation-induced changes were observed on MR images in three patients; one had symptoms attributable to these changes.

CONCLUSIONS
Gamma Knife surgery is an effective treatment for persistent Cushing's disease. Adenomas with cavernous sinus invasion that are not amenable to resection are treatable with the Gamma Knife. A second GKS treatment appears to increase the risk of cranial nerve damage. These results demonstrate the value of combining two neurosurgical treatment modalities-microsurgical resection and GKS-in the management of pituitary adenomas.
OBJECTIVE
Though transsphenoidal surgery remains the first-line treatment of Cushing's disease, recurrence occurs frequently. Conventional radiotherapy and anticortisolic drugs both have adverse effects. Stereotactic radiosurgery needs to be evaluated more precisely. The aim of this study was to determine long-term hormonal effects and tolerance of gamma knife (GK) radiosurgery in Cushing's disease.

DESIGN
Forty patients with Cushing's disease treated by GK were prospectively studied over a decade, with a mean follow-up of 54.7 months. Eleven of them were treated with GK as a primary treatment.

METHODS
Radiosurgery was performed at the Department of Functional Neurosurgery of Marseille, France, using the Leksell Gamma Unit B and C models. Median margin dose was 29.5 Gy. Patients were considered in remission if they had normalized 24-h free urinary cortisol and suppression of plasma cortisol after low-dose dexamethasone suppression test.

RESULTS
Seventeen patients (42.5%) were in remission after a mean of 22 months (range 12-48 months). The two groups did not differ in terms of initial hormonal levels. Target volume was significantly higher in uncured than in remission group (909.8 vs 443 mm³, P = 0.038). We found a significant difference between patients who were on or off anticortisolic drugs at the time of GK (20 vs 48% patients in remission respectively, P = 0.02).

CONCLUSION
With 42% of patients in remission after a median follow-up of 54 months, GK stereotactic radiosurgery, especially as an adjunctive treatment to surgery, may represent an alternative to other therapeutic options in view of their adverse effects.
**Front Horm Res. 2006;34:185-205.**
Stereotactic radiosurgery for pituitary adenomas: a review of the literature and our experience.
Sheehan JP, Jagannathan J, Pouratian N, Steiner L.

Lars Leksell Gamma Knife Center, Department of Neurological Surgery, Health Sciences Center, University of Virginia, Charlottesville, VA 22908, USA.

**Abstract**
Pituitary adenomas are not just one of the most common intracranial tumors but also one of the most difficult to cure. Neurosurgeons have adapted their tools to include precise ionizing radiation in the form of the gamma knife to treat pituitary adenomas. The use of the gamma knife in the management of pituitary adenomas following microsurgery or in selected cases as a primary treatment is safe. The combined application of transsphenoidal surgery and Gamma Knife surgery is beneficial in many difficult cases. However in some patients, optimal control of tumor growth and normalization of hypersecretory states are not achieved. Innovative improvements in operative and radiosurgical techniques are required to avoid pituitary insufficiency and to reduce the number of the cases in which optimal radiosurgery is not feasible because of close tumor proximity to the optic pathways.

---

**J Neurosurg. 2005 Jan;102 Suppl:119-23.**
Long-term results of gamma knife surgery for growth hormone-producing pituitary adenoma: is the disease difficult to cure?
Kobayashi T, Mori Y, Uchiyama Y, Kida Y, Fujitani S.

Radiosurgery Center, Nagoya Kyoritsu Hospital and Gamma Knife Center, Komaki City Hospital, Nagoya, Japan. ttkobayashi@kaikou.or.jp

**OBJECT**
The authors conducted a study to determine the long-term results of gamma knife surgery for residual or recurrent growth hormone (GH)-producing pituitary adenomas and to compare the results with those after treatment of other pituitary adenomas.

**METHODS**
The series consisted of 67 patients. The mean tumor diameter was 19.2 mm and volume was 5.4 cm³. The mean maximum dose was 35.3 Gy and the mean margin dose was 18.9 Gy. The mean follow-up duration was 63.3 months (range 13-142 months). The tumor resolution rate was 2%, the response rate 68.3%, and the control rate 100%. Growth hormone normalization (GH < 1.0 ng/ml) was found in 4.8%, nearly normal (< 2.0 ng/ml) in 11.9%, significantly decreased (< 5.0 ng/ml) in 23.8%, decreased in 21.4%, unchanged in 21.4%, and increased in
Serum insulin-like growth factor (IGF)-1 was significantly decreased (IGF-1 < 400 ng/ml) in 40.7%, decreased in 29.6%, unchanged in 18.5%, and increased in 11.1%, which was almost parallel to the GH changes.

**CONCLUSIONS**

Gamma knife surgery was effective and safe for the control of tumors; however, normalization of GH and IGF-1 secretion was difficult to achieve in cases with large tumors and low-dose radiation. Gamma knife radiosurgery is thus indicated for small tumors after surgery or medication therapy when a relatively high-dose radiation is required.

**Neurosurg Focus. 2004 Apr 15;16(4):E5.**
Stereotactic radiosurgery for Cushing disease.
Hentschel SJ, McCutcheon IE.

Department of Neurosurgery, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030-4009, USA.

The most common cause of Cushing syndrome is Cushing disease, in which hypercortisolism is produced by a functional adrenocorticotropic hormone-producing adenoma of the anterior pituitary gland. The common therapies available include microsurgical resection, conventional fractionated radiotherapy, and stereotactic radiosurgery (SRS). In this article the authors review the indications, results, and complications associated with SRS in the treatment of Cushing disease. In as many as 90% of patients SRS results in disease remission, which is defined as a normal 24-hour urinary free cortisol level and a normal or subnormal morning serum cortisol level. Although in most patients who are subsequently cured a marked decrease in the serum cortisol level is demonstrated within 3 months after treatment, a biochemical cure may be delayed up to 3 years in some cases. Complications following SRS for pituitary adenomas are uncommon, particularly in patients with microadenomas, which are most commonly seen in Cushing disease. The most common complication is hypopituitarism, which occurs in up to 50% of patients with a mean latency period of 5 years. Radiation-induced optic neuropathy has been reported in less than 2% of cases and induction of a secondary neoplasm in less than 1% of cases. For patients with Cushing disease, the rate of endocrinological cure following SRS appears to be similar to that attained using microsurgical resection. In contrast to surgery, SRS has the benefit of being noninvasive and associated with a very low incidence of diabetes insipidus, although hypopituitarism may be more common with SRS. With continued follow-up patient reviews and additional experience with SRS, it may become possible to make more definitive statements regarding SRS as the initial treatment for patients with Cushing disease.
Neurosurg Focus. 2007;23(3):E8

Treatment options for Cushing disease after unsuccessful transsphenoidal surgery.
Liu JK, Fleseriu M, Delashaw JB Jr, Ciric IS, Couldwell WT.

Department of Neurological Surgery, Northwestern University Feinberg School of Medicine, Evanston Northwestern Healthcare, Evanston, Illinois 60201, USA.

Cushing disease is considered an aggressive pituitary endocrinopathy because of the devastating effects from untreated hypercortisolemia. Although they are histologically benign, these adrenocorticotropic hormone (ACTH)-secreting pituitary tumors are associated with significant morbidity and premature death. Currently, transsphenoidal surgery is the primary treatment of Cushing disease associated with an ACTH-secreting pituitary tumor, resulting in remission rates ranging from about 50 to 90%. Some patients, however, will not achieve sustained remission after transsphenoidal surgery and can exhibit persistent or recurrent Cushing disease that requires multimodal treatment to achieve remission. In these patients, options for treatment include repeat transsphenoidal resection, radiation therapy (including conventional fractionated radiation therapy and stereotactic radiosurgery), and medical therapy. Despite undergoing multiple treatment modalities, some patients may ultimately require bilateral adrenalectomy for definitive treatment to eliminate hypercortisolemia associated with Cushing disease. In this article, the authors review the treatment options for patients who have persistent or recurrent Cushing disease after unsuccessful transsphenoidal surgery. The indications, current results reported in the literature, and complications of each treatment modality are discussed.


Kobayashi T, Kida Y, Mori Y.

Department of Neurosurgery, Gamma Knife Center, Komaki City Hospital, Komaki City, Japan.
ctkoby@mis.ne.jp

OBJECT
The authors sought to analyze the long-term outcome of patients with Cushing disease who underwent gamma knife radiosurgery (GKS) as either an adjuvant or primary treatment.

METHODS
Twenty-five patients with Cushing disease were treated by OKS and followed for more than 2.5 years (mean 5.3 years). The overall results showed a complete response rate of 30%, a response rate of 85%, and a tumor control rate of 100%. Tumor size and radiation dose were
the most important factors related to the treatment response. The complete response rate for microadenomas and small adenomas was significantly higher than that for macroadenomas. An 83.2% complete response rate was obtained using a maximum dose of more than 55 Gy and/or a margin dose of more than 40 Gy. Serum adrenocorticotropic hormone and cortisol levels were normalized in 35% of patients, decreased significantly in 60%, and decreased in 85%. Fifty-one of 85 characteristic signs and symptoms of Cushing disease improved without any side effects. The overall outcome was excellent in seven cases, good in six, fair in four, and poor in four cases; one patient died. The initial treatment was GKS in four patients, two of whom had a complete response and two of whom had a partial response. Hormone levels returned to normal in the patients in whom there was a complete response. The results in the six patients in whom Nelson syndrome was present were less favorable; the response rate was only 33%, although the control rate was 100%. Hormone levels decreased in two patients.

CONCLUSIONS
Gamma knife radiosurgery is safe and effective for the treatment of Cushing disease as an adjuvant or initial therapy when selective and accurate dose planning is performed.

Cushing's disease resulting from pituitary corticotrophic microadenoma. Treatment results from transsphenoidal microsurgery and gamma knife radiosurgery.
Laws ER, Reitmeyer M, Thapar K, Vance ML.

Department of Neurosurgery, University of Virginia, Charlottesville, VA 22908-0212, USA.
ELS9@virginia.edu

Cushing's disease and its associated clinical syndrome reflect the effects of excess cortisol on the individual. The cause of Cushing's disease is ordinarily an ACTH-secreting benign pituitary adenoma. The diagnosis of Cushing's disease is established by sophisticated endocrine testing and comprehensive imaging studies. Because of the devastating effects of excess cortisol, therapy that provides prompt and effective normalization of serum cortisol is essential. Currently this goal is best achieved by transsphenoidal microsurgery. This paper reviews the clinical presentation, laboratory analysis, surgical management and outcome in patients with Cushing's disease.
Radiosurgery for Cushing's disease after failed transsphenoidal surgery.

Department of Neurological Surgery, University of Virginia, Charlottesville, USA.

OBJECT
Although transsphenoidal surgery has become the standard of care for Cushing's disease, it is often unsuccessful in normalizing cortisol production. In this study the authors investigate the safety and efficacy of gamma knife radiosurgery (GKRS) for Cushing's disease after failed transsphenoidal surgery.

METHODS
The records of all patients who underwent GKRS at the authors' institution after unsuccessful transsphenoidal surgery for Cushing's disease were retrospectively reviewed. Successful treatment was considered a normal or below-normal 24-hour urinary free cortisol (UFC) level. Records were also evaluated for relapse, new-onset endocrine deficiencies, interval change in tumor size, and visual complications. Forty-three patients underwent 44 gamma knife procedures with follow up ranging from 18 to 113 months (mean 39.1, median 44 months). Normal 24-hour UFC levels were achieved in 27 patients (63%) at an average time from treatment of 12.1 months (range 3-48 months). Three patients had a recurrence of Cushing's disease at 19, 37, and 38 months, respectively, after radiosurgery. New endocrine deficiencies were noted in seven patients (16%). Follow-up magnetic resonance images obtained in 33 patients revealed a decrease in tumor size in 24, no change in nine, and an increase in size in none of the patients. One patient developed a quadrantanopsia 14 months after radiosurgery despite having received a dose of only 0.7 Gy to the optic tract.

CONCLUSIONS
Gamma knife radiosurgery appears to be safe and effective for the treatment of Cushing's disease refractory to pituitary surgery. Delayed recurrences and new hormone deficiencies may occur, indicating the necessity for regular long-term follow up.

Selected Literature 2003-2011: Gamma Knife Radiosurgery for (non-secreting) Pituitary Adenoma

Long-term outcomes after Gamma Knife radiosurgery for patients with a nonfunctioning pituitary adenoma.
Gopalan R, Schlesinger D, Vance ML, Laws E, Sheehan J.
Department of Neurological Surgery, University of Virginia, Charlottesville, Virginia, USA.

BACKGROUND
Nonfunctioning pituitary adenomas recur after microsurgery. Gamma Knife radiosurgery (GKRS) has been used to treat recurrent adenomas.

OBJECTIVE
To evaluate the long-term rates of tumor control and development of hypopituitarism in patients with nonfunctioning pituitary adenomas after GKRS.

METHODS
Forty-eight patients with a nonfunctioning pituitary adenoma treated between 1991 and 2004 at the University of Virginia were studied. All patients had more than 4 years of clinical and imaging follow-up.

RESULTS
All patients underwent follow-up imaging and endocrine evaluations, with a duration ranging from 50 to 215 months (median, 80.5 months) and 57 to 201 months (median, 95 months), respectively. New hormone deficiency after GKRS occurred in 19 of 48 patients (39%). Corticotropin/cortisol deficiency developed in 8% of patients, thyroid hormone deficiency in 20.8%, gonadotropin deficiency in 4.2%, growth hormone/insulin-like growth factor 1 in 16.7%, and diabetes insipidus in 2%. Panhypopituitarism including diabetes insipidus developed in 1 patient. Overall, control of tumor volume was 83%.
Tumor volume decreased in 36 patients (75%), increased in 8 patients (17%), and was unchanged in 4 patients (8%). Tumor volumes greater than 5 mL at the time of GKRS were associated with a significantly greater rate of growth (P = .003) compared with an adenoma with a volume of 5 mL or less.

CONCLUSION
GKRS resulted in a high and durable rate of tumor control in patients with a nonfunctioning pituitary adenoma. A higher preoperative tumor volume was associated with an increased rate of tumor growth.
BACKGROUND
Nonfunctional pituitary adenomas (NFPAs) represent approximately 50% of all pituitary tumors.

OBJECTIVE:
To evaluate the long-term outcomes of stereotactic radiosurgery for NFPAs.

METHODS
We evaluated the management outcomes of Gamma Knife radiosurgery in 125 patients with NFPAs over an interval of 22 years. The median patient age was 54 years (range, 16-88 years). One hundred ten patients (88%) had residual or recurrent tumors after ≥ 1 surgical procedures, and 17 (14%) had undergone prior fractionated radiation therapy. The median target volume was 3.5 cm³ (range, 0.4-28.1 cm³), and the median tumor margin dose was 13.0 Gy (range, 10-25 Gy).

RESULTS
Tumor volume decreased in 66 patients (53%), remained stable in 46 (37%), and increased in 13 (10.4%) during a median of 62 months (maximum, 19 years) of imaging follow-up. The actuarial tumor control rates at 1, 5, and 10 years were 99%, 94%, and 76%, respectively. Factors associated with a reduced progression-free survival included larger tumor volume (≥ 4.5 cm³) and ≥ 2 prior recurrences. Of 88 patients with residual pituitary function, 21 (24%) suffered new hormonal deficits at a median of 24 months (range, 3-114 months). Prior radiation therapy increased the risk of developing new pituitary hormonal deficits. One patient (0.8%) had a decline in visual function, and 2 (1.6%) developed new cranial neuropathies without tumor progression.

CONCLUSION
Stereotactic radiosurgery can provide effective management for patients with newly diagnosed NFPAs and for those after prior resection and/or radiation therapy.

Pituitary insufficiency as a side effect after radiosurgery for pituitary adenomas: the role of the hypothalamus.
Feigl GC, Pistracher K, Berghold A, Mokry M.

Department of Neurosurgery, University of Tuebingen Medical Center, Germany. guenther.feigl@web.de

BACKGROUND
Causes of pituitary insufficiencies as a side effect of Gamma Knife surgery (GKS) following irradiation of the hypothalamopituitary axis are still under debate. In an investigation of pituitary insufficiencies after GKS, the authors' main focus is on what role can be attributed to the hypothalamus with regard to endocrinological changes in hypothalamopituitary function following GKS.
METHODS
A total of 108 patients consecutively treated between April 1992 and July 2003 were included in this retrospective study. All patients had undergone either transsphenoidal or transcranial surgery prior to GKS. The spot dosimetry method was used to determine doses delivered to structures of the hypothalamopituitary axis. For statistical analyses, endocrine insufficiency and deterioration in pituitary function were defined as a decrease in hormonal blood levels below the normal range for 1 or more anterior pituitary lobe hormones. Additionally, an analysis of the rate of patients requiring hormone replacement therapy after GKS due to new endocrinopathies was performed.

Complete patient records of 61 male and 47 female patients with a mean age of 51.9 years (range 9.1–81.2 years) were available for our investigation. The overall tumor control rate was 97% and the endocrinological cure rate was 61.2%. Mean treatment doses in patients with and without new endocrine insufficiencies (shown as with/without insufficiencies and followed by probability values) were as follows: 1.3/0.8 Gy to the hypothalamus (p = 0.2); 2.2/1.6 Gy to the median eminence (p = 0.1); 6.5/4.1 Gy to the pituitary stalk (p = 0.004); and 12.4/9.5 Gy to the pituitary gland (p = 0.05). The median overall duration of follow-up after GKS was 6.7 years, with 84 patients (77.7%) whose follow-up was longer than 12 months. The median follow-up time after GKS in patients who developed a new pituitary dysfunction was 79.5 months (6.6 years, SD 3.8 years), and the median follow-up time in patients with no new insufficiencies was 78.4 months (6.5 years, SD 4 years).

Gamma Knife surgery is a safe and effective treatment for patients with residual and recurrent pituitary adenomas. The rate of pituitary insufficiencies after GKS is still lower than that after conventional radiotherapy. Very low radiation doses are directed to the hypothalamus, and thus this structure does not play a major role in the development of pituitary insufficiencies after GKS. The results of this study show that patients in whom the pituitary stalk and pituitary gland receive a high mean point dose are more likely to develop pituitary insufficiencies after GKS than those who receive a lower dose.

Is it possible to avoid hypopituitarism after irradiation of pituitary adenomas by the Leksell gamma knife?
Marek J, Jezková J, Hána V, Krsek M, Bandúrová L, Pecen L, Vladyka V, Liscák R.

Third Department of Medicine, First Medical Faculty, Charles University, Czech Republic.

BACKGROUND
Radiation therapy is one of the treatment options for pituitary adenomas. The most common side effect associated with Leksell gamma knife (LGK) irradiation is the development of hypopituitarism. The aim of this study was to verify that hypopituitarism does not develop if the maximum mean dose to pituitary is
kept under 15 Gy and to evaluate the influence of maximum distal infundibulum dose on the development of hypopituitarism.
METHODS
We followed the incidence of hypopituitarism in 85 patients irradiated with LGK in 1993-2003. The patients were divided in two subgroups: the first subgroup followed prospectively (45 patients), irradiated with a mean dose to pituitary <15 Gy; the second subgroup followed retrospectively 1993-2001 and prospectively 2001-2009 (40 patients), irradiated with a mean dose to pituitary >15 Gy. Serum TSH, free thyroxine, testosterone or 17β-oestadiol, IGF1, prolactin and cortisol levels were evaluated before and every 6 months after LGK irradiation.

RESULTS
Hypopituitarism after LGK irradiation developed only in 1 out of 45 (2.2%) patients irradiated with a mean dose to pituitary <15 Gy, in contrast to 72.5% patients irradiated with a mean dose to pituitary >15 Gy. The radiation dose to the distal infundibulum was found as an independent factor of hypopituitarism with calculated maximum safe dose of 17 Gy.

CONCLUSION
Keeping the mean radiation dose to pituitary under 15 Gy and the dose to the distal infundibulum under 17 Gy prevents the development of hypopituitarism following LGK irradiation.

Role of stereotactic radiosurgery in the management of pituitary adenomas.
Castinetti F, Régis J, Dufour H, Brue T.
Centre de Référence des Maladies Rares d’Origine Hypophysaire, Service d’Endocrinologie, Diabète et Maladies Métaboliques, Hôpital de la Timone, Assistance Publique Hôpitaux de Marseille, Rue St Pierre, Université de la Mediterranean, Marseille Cedex 05, France. fredcast@umich.edu

Trans-sphenoidal neurosurgery is the gold standard treatment for pituitary adenomas, but it can be contraindicated or ineffective. Stereotactic radiosurgery is a procedure aimed at controlling hormone hypersecretion and tumor size of pituitary adenomas. This Review discusses the long-term efficacy and adverse effects of stereotactic radiosurgery with the Gamma Knife(R) in secreting and nonsecreting pituitary adenomas. Long-term data confirm the antisecretory efficacy of the procedure (about 50% remission in hypersecreting tumors) but also a previously unknown low risk of recurrence (2-10% of cases). The time to remission is estimated to range from 12 to 60 months. The antitumoral efficacy of this treatment against nonsecreting tumors is observed in about 90% of cases. Hypopituitarism is the main adverse effect, observed in 20-40% of cases. Comparisons with conventional fractionated radiotherapy reveal a lower rate of remission with Gamma Knife(R) radiosurgery, counterbalanced by a more rapid efficacy and a lower rate of hypopituitarism. Short-term follow-up results on stereotactic fractionated radiotherapy suggest a risk of hypopituitarism similar to
the one observed with radiosurgery. Therefore, stereotactic radiosurgery is probably still useful to treat some cases of pituitary adenoma, despite the fact that antisecretory drugs, particularly for acromegaly and prolactinomas, are becoming more effective and are well tolerated, thus increasing the probability of success with nonsurgical therapy.

Stereotactic radiosurgery for pituitary adenomas: a comprehensive review of indications, techniques and long-term results using the Gamma Knife.
Jagannathan J, Yen CP, Pouratian N, Laws ER, Sheehan JP.
Department of Neurological Surgery, University of Virginia Health Sciences Center, Box 800212, Charlottesville, VA 22908, USA. jj5a@virginia.edu

This study reviews the long-term clinical results of stereotactic radiosurgery in the treatment of pituitary adenoma patients.

METHODS
We reviewed the outcomes of 298 patients who underwent Gamma Knife radiosurgery for recurrent or residual pituitary adenomas. These results are compared to other contemporary radiosurgical series.

RESULTS
Pituitary tumors are well-suited for radiosurgery, since radiation can be focused on a well circumscribed region, while adjacent neural structures in the suprasellar and parasellar regions are spared. The overall rate of volume reduction following stereotactic radiosurgery is 85% for non-secretory adenomas that are followed for more than 1-year. The rates of hormonal normalization in patients with hypersecretory adenomas can vary considerably, and tends to be higher in patients with Cushing's Disease and acromegaly (remission rate of approximately 53% and 54%, respectively) when compared with patients who have prolactinomas (24% remission) and Nelson's syndrome (29%) remission. Advances in dose delivery and modulation of adenoma cells at the time of radiosurgery may further improve results.

CONCLUSIONS
Although the effectiveness of radiosurgery varies considerably depending on the adenoma histopathology, volume, and radiation dose, most studies indicate that radiosurgery when combined with microsurgery is effective in controlling pituitary adenoma growth and hormone hypersecretion. Long-term follow-up is essential to determine the rate of endocrinopathy, visual dysfunction, hormonal recurrence, and adenoma volume control.
**Pituitary. 2009;12(3):211-6.**  
Adjuvant Gamma Knife radiosurgery in non-functioning pituitary adenomas; low risk of long-term complications in selected patients.  
Höybye C, Rähn T.  
Department of Endocrinology, Karolinska University Hospital, 171 76 Solna, Stockholm, Sweden. charlotte.hoybye@karolinska.se

**Abstract**  
Complete surgical removal of non-functioning pituitary adenomas is often not possible. This retrospective study aimed at evaluating the long-term outcome and complications of Gamma Knife (GK) radiosurgery adjuvant to pituitary microsurgery in selected patients with small tumour remnants treated 1994-2004. **Thirteen men and ten women**, median age 49 years, were identified. Prior to GK 15 patients had remaining pituitary function. Median size of the tumours was 1.1 cm(3). Median **marginal dose was 20 Gy**. Median follow-up with MR imaging was 78 and 97 months for clinical evaluation. Tumour growth control was 100%, irrespectively of growth hormone (GH) therapy for 72 months (n = 10). Only one recurrence was discovered outside radiation field and no new hypopituitarism was developed. This report suggests that in well-selected patients the long-term risk of complications is low and with careful surveillance GH insufficiency can be replaced. Lifelong follow-up is mandatory.

**Prog Neurol Surg. 2009;22:77-95.**  
Long-term results of stereotactic gamma knife radiosurgery for pituitary adenomas. Specific strategies for different types of adenoma.  
Kobayashi T.  
Nagoya Radiosurgery Center, Nagoya Kyoritsu Hospital, Nagoya, Aichi, Japan. ttkobayashi@kaikou.or.jp

**Abstract**  
Long-term results of gamma knife radiosurgery for pituitary adenomas are presented and treatment strategies for different adenoma types are discussed. Two hundred and sixty-seven patients with pituitary adenoma have been treated by gamma knife radiosurgery during the past 12 years. There were **131 cases of nonfunctioning and 136 cases of functioning adenomas**, in which 71 GH-producing, 33 PRL-producing and 32 ACTH-producing adenomas were included. Retreatment with the gamma knife was done in 8 cases because of large tumors or uncontrolled hormones. Micro- and small adenomas could be cured by gamma knife radiosurgery alone. Surgical or chemical debulking was necessary before radiosurgery for a large tumor with extrasellar extension. Retreatment was effective and safe in some cases. Nonfunctioning adenomas showed higher control rates than functioning
adenomas even with lower dose treatment. Cushing disease showed the best response because of the smallest tumor size with the highest dose treatment. Acromegaly and prolactinoma were difficult to control because of larger tumors with lower dose treatment. The rate of hormone normalization was also high in Cushing disease but lower in prolactinoma and lowest in acromegaly. High-dose treatment was necessary for functioning adenomas to control tumor growth and oversecretion of hormones. In conclusion, gamma knife radiosurgery was effective and safe for the treatment of pituitary adenomas. However, the treatment strategies should be specific to each adenoma type according to the radiosensitivity, chemosensitivity and biological nature of the tumor.


Gamma knife radiosurgery for patients with nonfunctioning pituitary adenomas: results from a 15-year experience.


Department of Neurological Surgery, Mayo Clinic College of Medicine, Rochester, MN 55905, USA.
pollock.bruce@mayo.edu

**PURPOSE**

To evaluate the efficacy and complications of stereotactic radiosurgery for patients with nonfunctioning pituitary adenomas (NFA).

**METHODS AND MATERIALS**

This was a retrospective review of 62 patients with NFA undergoing radiosurgery between 1992 and 2004, of whom 59 (95%) underwent prior tumor resection. The median treatment volume was 4.0 cm(3) (range, 0.8-12.9). The median treatment dose to the tumor margin was 16 Gy (range, 11-20). The median maximum point dose to the optic apparatus was 9.5 Gy (range, 5.0-12.6). The median follow-up period after radiosurgery was 64 months (range, 23-161).

**RESULTS**

Tumor size decreased for 37 patients (60%) and remained unchanged for 23 patients (37%). Two patients (3%) had tumor growth outside the prescribed treatment volume and required additional treatment (fractionated radiation therapy, n = 1; repeat radiosurgery, n = 1). Tumor growth control was 95% at 3 and 7 years after radiosurgery. Eleven (27%) of 41 patients with normal (n = 30) or partial (n = 11) anterior pituitary function before radiosurgery developed new deficits at a median of 24 months after radiosurgery. The risk of developing new anterior pituitary deficits at 5 years was 32%. The 5-year risk of developing new anterior pituitary deficits was 18% for patients with a tumor volume of < or = 4.0 cm(3) compared with 58% for patients
with a tumor volume >4.0 cm(3) (risk ratio = 4.5; 95% confidence interval = 1.3-14.9, p = 0.02). No patient had a decline in visual function.
CONCLUSIONS
Stereotactic radiosurgery is effective in the management of patients with residual or recurrent NFA, although longer follow-up is needed to evaluate long-term outcomes. The primary complication is hypopituitarism, and the risk of developing new anterior pituitary deficits correlates with the size of the irradiated tumor.

Gamma knife radiosurgery for endocrine-inactive pituitary adenomas.
Liscák R, Vladyka V, Marek J, Simonová G, Vymazal J.
Stereotactic and Radiation Neurosurgery, Na Homolce Hospital, Prague, Czech Republic.
roman.liscak@homolka.cz

BACKGROUND
The goal of nonsecreting pituitary adenoma radiosurgery is to halt tumour growth and to maintain normal performance of the hypophysis and the functionally important structures around the sella. The effectiveness of gamma knife radiosurgery was evaluated.

METHOD
Over a period of 10 years (1993-2003), 140 patients with nonsecreting pituitary adenoma were treated by Leksell gamma knife at our Centre. Seventy-nine of them were followed up for longer than 3 years. Their age range was 24-73 years, with a median of 54 years. Eighty-five percent of them had previous open surgery. Fifteen patients had adenoma contact with the optic tract. Fourteen patients had a normally functioning hypophysis, 48 patients had complete panhypopituitarism, while the rest retained partial functions of the normal hypophysis. Adenoma volumes ranged between 0.1 and 31.3, the median being 3.45 ccm. The marginal dose ranged between 12 and -35 Gy, with a median of 20 Gy.

FINDINGS
The follow-up ranged from 36 to 122 months, with a median of 60 months. No adenoma growth was detected; 89% of treated adenomas decreased in size, with a median volume reduction of 61%. There was no perimeter vision impairment after radiosurgery, while 4 out of 52 patients with abnormal perimeter vision reported improvement. There was no impairment of oculomotor nerve function. Impairment of hypophysis function was observed in 2 patients.

CONCLUSIONS
Radiosurgery has a reliable antiproliferative effect on nonsecreting pituitary adenomas. It is a safe treatment with a low risk of morbidity. Short contact between a nonsecreting pituitary adenoma and the optic pathway is not an absolute contraindication for Gamma knife radiosurgery.

**J Neurosurg. 2006 Jun;104(6):876-83.**

Gamma surgery in the treatment of nonsecretory pituitary macroadenoma.

Mingione V, Yen CP, Vance ML, Steiner M, Sheehan J, Laws ER, Steiner L.

Department of Neurological Surgery, Lars Leksell Center for Gamma Surgery, University of Virginia Health System, Charlottesville, Virginia 22908, USA.

**OBJECT**

The authors report on a retrospective analysis of the imaging and clinical outcomes following gamma surgery in 100 patients with nonsecretory pituitary macroadenoma.

**METHODS**

Between June 1989 and March 2004, **100 consecutive patients with nonsecretory pituitary macroadenoma** were treated at the Lars Leksell Center for Gamma Surgery, University of Virginia Health System (Charlottesville, VA). Ninety-two patients had residual or recurrent macroadenoma following one or more surgical procedures. In eight patients, gamma surgery was the primary treatment. Ten patients received conventional fractionated radiotherapy before the gamma surgery. Sixty-nine patients required hormone replacement therapy for one or more deficits before gamma knife treatment. Peripheral doses between 5 and 25 Gy (mean 18.5 Gy) were administered. Imaging and endocrinological follow-up evaluations were performed in 90 patients; these studies ranged from 6 to 142 months (mean 44.9 months) and 6 to 127 months (mean 47.9 months), respectively. **Tumor volume decreased in 59 patients (65.6%), remained unchanged in 24 (26.7%), and increased in seven (7.8%).** The minimal effective peripheral dose was 12 Gy; peripheral doses greater than 20 Gy did not seem to provide additional benefit. Of 61 patients with a partially or fully functioning pituitary gland and follow-up data, 12 (19.7%) suffered new hormone deficits following gamma surgery. In patients with endocrinological follow-up data that had been collected over more than 2 years, the rate of new deficits was 25%. No neurological morbidity or death was related to treatment. **CONCLUSIONS:** Current experience suggests that gamma surgery is an appropriate means of managing recurrent or residual nonsecretory pituitary macroadenoma following microsurgery and a primary treatment in selected patients. To evaluate definite rates of recurrence and new endocrine deficiencies, long-term follow-up studies are needed.
Radiosurgery for nonfunctioning pituitary adenoma.
Sheehan JP, Kondziolka D, Flickinger J, Lunsford LD.

Department of Neurosurgical Surgery, University of Virginia Health Sciences Center, Charlottesville 22908, USA. jps2f@virginia.edu

OBJECT
Nonfunctioning pituitary adenomas comprise approximately 30% of all pituitary tumors. The purpose of this retrospective study was to evaluate the efficacy and role of gamma knife surgery (GKS) in the treatment of these lesions.

METHODS
The authors conducted a review of cases in which GKS was performed at the University of Pittsburgh between 1987 and 2001. Forty-six patients with nonfunctioning pituitary adenomas and with at least 6 months of follow-up data were identified. In 41 of these patients some form of prior treatment such as transsphenoidal resection, craniotomy and resection, or conventional radiation therapy had been conducted. Five patients were deemed ineligible for microsurgery, and GKS served as the primary treatment modality. Endocrinological, ophthalmological, and radiological responses were evaluated. The mean radiation dose to the margin was 16 Gy. In all patients with microadenomas and 91% of those with macroadenomas tumor control was demonstrated after radiosurgery. Gamma knife surgery had essentially equal efficacy in terms of achieving tumor control in cases of adenomas with cavernous sinus invasion and suprasellar extension. No new endocrinopathies were noted following radiosurgery. In two patients, however, tumor growth and decline in visual function occurred.

CONCLUSIONS
Gamma knife surgery is safe and effective in treating nonfunctioning pituitary adenomas. Radiosurgery may serve as a primary treatment modality in some or as a salvage treatment in others. Treatment must be tailored to meet the patient's symptoms, overall health, and tumor morphometry.
6. Gamma Knife Radiosurgery for glioma

Gamma Knife radiosurgery may constitute an alternative late option after the standard treatment has failed and has been applied in worldwide more than 27,000 patients with malignant gliomas and more than 4500 patients with benign gliomas.

Surgical debulking is the mainstay of initial treatment, but surgery alone is inadequate for obtaining reliable tumor control. Conventional fractionated radiation is generally applied as standard treatment of malignant glioma, but regularly results in tumour recurrences in virtually all treated patients.

For patients with malignant glioma, there is Level I-III evidence that the use of radiosurgery boost followed by external beam radiotherapy and BCNU does not confer benefit in terms of overall survival, local brain control, or quality of life as compared with external beam radiotherapy and BCNU, but Gamma Knife radiosurgery is used as local treatment of malignant gliomas in cases where an open tumor resection is impossible or in cases of postoperative recurrences of conventionally treated patients. Hence stereotactic radiosurgery with Gamma Knife can provide additional tumour control in cases of glioma recurrences after the standard therapy with resection and fractionated radiotherapy.

Several studies have shown that the addition of a Gamma Knife stereotactic radiosurgery boost in recurrences significantly improved the overall survival time of glioma patients. The addition of a Gamma Knife radiosurgery boost in conjunction with surgery and WBRT significantly improved the overall survival time in a study of patients with GBM (25 vs 13 months) (Nwokedi EC et al: Neurosurgery 2002 Jan;50 (1):41-6; discussion 46-7).

Survival after radiosurgery for glioma is strongly related to five selection variables (grading, age, decreased KPS, increased volume, multifocality). Much of variation in survival reported can be attributed to differences of these variables. The median survival of patients with primary glioblastoma after Gamma Knife treatment was 86 weeks (if brachytherapy criteria were satisfied) (D.Larson et al. : Gamma Knife for Glioma: Selection Factors and Survival Int J Radiat Oncol Biol Phys, Vol 36, No.5, 1045-1053, 1996). For selected groups the outcome can be clearly improved by addition of radiosurgery. These selection criteria are best defined by the RTOG classes. Gamma knife radiosurgery increased the outcome of patients with anaplastic glioma clearly when compared with patients treated with conventional radiotherapy. This was demonstrated particularly for RTOG classes III and V where radiosurgery resulted in clearly increased median survival rate and 2-year survival rates when compared to historical RTOG analyses (D. Kondziolka et al: Neurosurg 41,4, 1997).

In pilocytic astrocytoma and ependymoma Gamma Knife radiosurgery can achieve long-term tumour control and allows avoiding surgical resection of smaller tumours.
Selected Literature 1996-2011: Gamma Knife Radiosurgery for Glioma

Efficacy of gamma knife radiosurgery for small-volume recurrent malignant gliomas after initial radical resection.
Elliott RE, Parker EC, Rush SC, Kalhorn SP, Moshel YA, Narayana A, Donahue B, Golfinos JG.
Department of Neurosurgery, New York University Langone Medical Center, New York, New York, USA.

OBJECTIVE
To review the authors' experience with Gamma Knife radiosurgery (GKR) for small recurrent high-grade gliomas (HGGs) following prior radical resection, external-beam radiation therapy (EBRT), and chemotherapy with temozolomide (TMZ).

METHODS
The authors retrospectively analyzed 26 consecutive adults (9 women and 17 men; median age 60.4 years; Karnofsky Performance Status [KPS]≥70) who underwent GKR for recurrent HGGs from 2004-2009. Median lesion volume was 1.22 cc, and median treatment dose was 15 Gy. Pathology included glioblastoma multiforme (GBM; n=16), anaplastic astrocytoma (AA; n=5), and anaplastic mixed oligoastrocytoma (AMOA; n=5). Two patients lost to follow-up were excluded from radiographic outcome analyses.

RESULTS
Median overall survival (OS) for the entire cohort from the time of GKR was 13.5 months. Values for 12-month actuarial survival from time of GKR for GBM, AMOA, and AA were 37%, 20% and 80%. Local failure occurred in 9 patients (37.5%) at a median time of 5.8 months, and 18 patients (75%) experienced distant progression at a median of 4.8 months. Complications included radiation necrosis in two patients and transient worsening of hemiparesis in one patient. Multivariate hazard ratio (HR) analysis showed KPS 90 or greater, smaller tumor volumes, and increased time to recurrence after resection to be associated with longer OS following GKR.

CONCLUSIONS
GKR provided good local tumor control in this group of clinically stable and predominantly high-functioning patients with small recurrent HGGs after radical resection. Meaningful survival times after GKR were seen. GKR can be considered for selected patients with recurrent HGGs.
**Technol Cancer Res Treat. 2011 Jun;10(3):253-8.**
Re-irradiation with radiosurgery for recurrent glioblastoma multiforme.
Torok JA, Wegner RE, Mintz AH, Heron DE, Burton SA.

**Source**
Department of Radiation Oncology, University of Pittsburgh Cancer Institute, UPMC Shadyside Hospital, 5150 Centre Avenue, #545 Pittsburgh, PA 15232, USA.

**Abstract**
Local tumor control remains a significant challenge in patients with glioblastoma multiforme (GBM). Despite aggressive radiation therapy approaches, most recurrences are within the high-dose field, limiting the ability to safely re-irradiate recurrence using conventional techniques. Fractionated stereotactic radiosurgery (fSRS) is a technique whose properties make it useful for re-irradiation. We retrospectively reviewed the charts of 14 patients with recurrent GBM treated with salvage radiosurgery. Seven patients were male and seven were female with a median age of 58 (range: 39-76). All patients had prior cranial radiation therapy to a median dose of 60 Gy (58-69). There were 18 lesions treated with a median tumor volume of 6.97 cm3 (0.54-50.0 cm3). fSRS was delivered in 1-3 fractions to a median dose of 24 Gy (18-30 Gy). Median follow-up for the cohort was 8 months (3-22 months). On follow-up MRI, 8 of 18 lesions had a radiographic response. The median time-to-progression following primary irradiation was 8 months (1-28 months) while the median time-to-progression (TTP) following fSRS was 5 months (1-16 months). Median local control following re-irradiation was 5 months and actuarial local control was 21% at 1-year. Overall survival following primary irradiation was 79% at 12 months and 46% at 2 years. Overall survival following re-irradiation was 79% at 6 months and 30% at 1 year. No significant treatment-related toxicity was seen in follow-up. These results indicate that re-irradiation for recurrent GBM using fSRS is well-tolerated and can offer a benefit in terms of progression-free survival (PFS).

Gamma Knife surgery for subependymal giant cell astrocytomas. Clinical article.
Park KJ, Kano H, Kondziolka D, Niranjan A, Flickinger JC, Lunsford LD.

Department of Neurological Surgery, University of Pittsburgh, Center for Image-Guided Neurosurgery, Pittsburgh, Pennsylvania, USA.

**OBJECT**
The authors report their experience of using Gamma Knife surgery (GKS) in patients with subependymal giant cell astrocytoma (SEGA).
METHODS
Over a 20-year period, the authors identified 6 patients with SEGAs who were eligible for GKS. The median patient age was 16.5 years (range 7-55 years). In 4 patients, GKS was used as a primary management therapy. One patient underwent radiosurgery for recurrent tumors after prior resection, and in 1 patient GKS was used as an adjunct after subtotal resection. The median tumor volume at GKS was 2.75 cm(3) (range 0.7-5.9 cm(3)). A median radiation dose of 14 Gy (range 11-20 Gy) was delivered to the tumor margin.

RESULTS
The median follow-up duration was 73 months (range 42-90 months). Overall local tumor control was achieved in 4 tumors (67%) with progression-free periods of 24, 42, 57, and 66 months. Three tumors regressed and one remained unchanged. In 2 patients the tumors progressed, and in 1 of these patients the lesion was managed by repeated GKS with subsequent tumor regression. The other relatively large tumor (5.9 cm(3)) was excised 9 months after GKS. The progression-free period for all GKS-managed tumors varied from 9 to 66 months. There were no cases of hydrocephalus or GKS-related morbidity.

CONCLUSIONS
Gamma Knife surgery may be an additional minimally invasive management option for SEGA in a patient who harbors a small but progressively enlarging tumor when complete resection is not safely achievable. It may also benefit patients with a residual or recurrent tumor that has progressed after surgery.

Early or delayed radiosurgery for WHO grade II astrocytomas.
Park KJ, Kano H, Kondziolka D, Niranjan A, Flickinger JC, Lunsford LD.
Department of Neurological Surgery, Center for Image-Guided Neurosurgery, University of Pittsburgh, Suite B-400, UPMC Presbyterian, 200 Lothrop Street, Pittsburgh, PA 15213, USA.

Abstract
To evaluate the role of gamma knife stereotactic radiosurgery (SRS) in the management of newly diagnosed (early) or progressive (delayed) WHO grade II astrocytomas, the authors reviewed 25 patients who underwent SRS for pathologically proven WHO grade II astrocytomas between 1987 and 2009 at the University of Pittsburgh. The median patient age was 30 years (range 8-68 years). Sixteen patients had early SRS after stereotactic biopsy (n = 14), resection (n = 1) or radiation therapy (n = 1), and 9 underwent delayed SRS for progression after surgical resection (n = 3), radiation therapy (n = 4) or both (n = 2). The median tumor volume was 3.7 cm(3) (range 0.6-17.0
cm(3)) and the median margin dose was 14 Gy (range 11-20 Gy). At a median of 65 months of follow-up (range 6-208 months), tumor control was observed in 13 patients (52%). The progression-free survival rates after SRS at 1, 5 and 10 years were 91.3, 54.1 and 37.1%, respectively. On both univariate and multivariate analysis smaller tumor volume (<6 cm(3)), higher marginal dose (≥15 Gy) and absence of contrast enhancement on imaging studies were associated with better progression free-survival. Gamma knife SRS is an additional option for patients with small volume, deep seated, non-enhancing and well-demarcated WHO grade II astrocytomas and does not preclude later conventional fractionated radiation therapy, cyst aspiration, or cautious debulking if feasible. It may also benefit patients with residual or recurrent tumors that have progressed after surgery, radiation therapy or both.

Stereotactic radiosurgery for pilocytic astrocytomas part 2: outcomes in pediatric patients.
Kano H, Niranjan A, Kondziolka D, Flickinger JC, Pollack IF, Jakacki RI, Lunsford LD.
Department of Neurological Surgery, University of Pittsburgh School of Medicine, Suite B-400, UPMC Presbyterian, 200 Lothrop Street, Pittsburgh, PA 15213, USA.

Abstract
To assess outcomes after stereotactic radiosurgery (SRS) for newly diagnosed or recurrent pilocytic astrocytomas in pediatric patients. Fifty patients (28 male and 22 females) with juvenile pilocytic astrocytomas (JPA) underwent Gamma knife SRS between 1987 and 2006. The median patient age was 10.5 years (range, 4.2-17.9 years). Three patients had failed prior fractionated radiation therapy (RT) and two had failed RT and chemotherapy. The median radiosurgery target volume was 2.1 cc (range, 0.17-14.4 cc) and the median margin dose was 14.5 Gy (range, 11-22.5 Gy). At a median follow-up of 55.5 months (range 6.0-190 months), one patient died and 49 were alive. The progression free survival after SRS (including tumor growth and cyst enlargement) for the entire series was 91.7, 82.8 and 70.8% at 1, 3 and 5 years, respectively. Stereotactic radiosurgery for pediatric pilocytic astrocytomas should be considered when resection is not feasible, or if there is an early recurrence. The best response was observed in small volume residual solid tumors.
Stereotactic radiosurgery for pilocytic astrocytomas part 1: outcomes in adult patients.
Kano H, Kondziolka D, Niranjan A, Flickinger JC, Lunsford LD.

Abstract
To assess outcomes when stereotactic radiosurgery (SRS) is used during multimodality management of pilocytic astrocytomas in adult patients. Fourteen patients (six male and eight females) with pilocytic astrocytomas underwent SRS between 1994 and 2006. The median patient age was 32 years (range, 19-52 years). Initial surgical management included stereotactic biopsy (N = 4), gross total resection (N = 1), and partial resection (N = 9). Fractionated radiation therapy had failed in six patients. The median radiosurgery target volume was 4.7 cc (range, 0.6-33.7 cc) and the median margin dose was 13.3 Gy (range, 10-20 Gy). At a median follow-up of 36.3 months (range 6.1-109 months), three patients died and 11 were alive. The overall survival after SRS for the entire series was 100%, 88.9% and 88.9% at 1, 3 and 5 years, respectively. Localized solid tumor progression was seen in two patients. Cyst progression was noted in three of nine patients with cystic tumors and mixed solid and cyst progression was noted in two with cystic tumors. The progression free survival after SRS (including tumor growth and cyst enlargement) for the entire series was 83.9%, 31.5% and 31.5% at 1, 3 and 5 years, respectively. Prior surgical resection was associated with better progression free survival after SRS (P = 0.027). Despite their purported benign nature, pilocytic astrocytomas in adult patients often do not behave benignly. Unresectable pilocytic astrocytomas that are located in critical or deep areas of the brain require additional management approaches. In this preliminary experience obtained over a 12 year interval, SRS is most valuable for patients after maximal feasible surgical resection. Delayed cyst progression contributes to late loss of tumor control.

Gamma Knife radiosurgery after radiation therapy as an adjunctive treatment for glioblastoma.
Pouratian N, Crowley RW, Sherman JH, Jagannathan J, Sheehan JP.

Despite a randomized trial showing no benefit of stereotactic radiosurgery (SRS) prior to radiation therapy (RT), the benefits of SRS after RT and at the time of progression require further characterization. We retrospectively reviewed 48 patients with histopathological diagnoses of
glioblastoma (GBM) that were treated with SRS over a 16-year period (1991-2007). Twenty-two were treated as part of their initial treatment paradigm and 26 were treated at the time of progression. The primary endpoints studied were overall survival (OS), survival after SRS and time-to-progression (TTP). **Patients treated at the time of progression had significantly longer OS than those treated on initial presentation (17.4 vs. 15.1 months, P = 0.003).** On multivariate analysis, Radiation Therapy Oncology Group (RTOG) class III patients, those with more extensive resections, and those who were not on steroids at the time of SRS had significantly improved OS. SRS margin dose was a significant prognostic factor for TTP on multivariate analysis (HR = 0.78, 95% CI: 0.62-0.98). In the subgroup of patients treated with GKS as part of their initial treatment, an increasing number of weeks between surgical resection and GKS was a poor prognostic factor on multivariate analysis (HR = 1.11, 95% CI: 1.01-1.23). In patients who were treated with SRS at the time of progression, chemotherapy was associated with a longer TTP (P = 0.028). Our results suggest that SRS provides a survival advantage when delivered after RT. This benefit may be best appreciated in RTOG class III patients. Moreover, SRS may be a viable alternative to open surgery for aggressive management of GBM at the time of recurrence. Prospective studies of SRS for GBM should focus on these two groups of patients.


Gamma knife stereotactic radiosurgery for low-grade astrocytomas.


**Source**

Department of Radiation Oncology, Indiana University Medical Center, Indianapolis, IN 46202, USA.

mahender@iupui.edu

**Abstract**

Patients with low-grade astrocytoma (LGA; 8 pilocytic astrocytomas, 2 subependymal giant cell astrocytomas, 2 fibrillary astrocytomas) were selected for treatment with gamma knife stereotactic radiosurgery (GKSRS) based on having a demarcated appearance on CT or MRI and the possibility of dose sparing of adjacent eloquent structures. A median dose of 13 Gy was prescribed to the 50% isodose line, which covered the gross tumor. The median patient age was 17.4 years. The median target volume was 4.4 cm(3). With a median follow-up of 48.2 months, 4-year tumor control and overall survival were 77 and 83%, respectively. Only 2 patients experienced symptomatic treatment-related toxicity. GKSRS can provide local control in cases of unresectable or recurrent LGA with a low incidence of side effects in carefully selected patients.
Objective
To develop outcome predictors after stereotactic radiosurgery (SRS) in patients with intracranial ependymomas who had received previous fractionated radiation therapy, we compared tumor control, survival, and complications with tumor grade, volume, age of patients, and imaging characteristics.

Methods
We retrospectively reviewed records of 39 consecutive ependymoma patients who underwent SRS for 56 tumors. The median patient age was 22.8 years (range, 2.9-71.1 years). All patients had previous surgical resection of their ependymomas followed by radiotherapy, and 14 patients underwent previous chemotherapy. Twenty-five patients had low-grade ependymomas (34 tumors), and 14 patients had anaplastic ependymomas (22 tumors). The median radiosurgery target volume was 3.6 cm (range, 0.1-36.8 cm), and the median margin dose was 15.0 Gy (range, 10-22 Gy).

Results
At a median of 23.5 months after SRS (range, 6.1-155.2 months), 25 patients died as a result of metastases (12 patients) or disease progression (13 patients). The overall survival rates after SRS were 60.1, 36.1, and 32.1% at 1, 3, and 5 years, respectively. The progression-free survival rates after SRS at 1, 3, and 5 years were 81.6, 45.8, and 45.8%, respectively, for all grades of ependymomas. Lower histological tumor grade was not significantly associated with better progression-free survival (P = 0.725). Factors associated with an improved progression-free survival included smaller tumor volume and homogeneous tumor contrast enhancement in low-grade ependymomas.

Conclusion
SRS provides another management option for patients with residual or recurrent ependymomas that have failed surgery and radiation therapy. Predictors of response include smaller volume and homogeneous contrast enhancement.
Does radiosurgery have a role in the management of oligodendrogliomas?

Departments of Neurological Surgery, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania 15213, USA.

OBJECT
In this study the authors evaluated the role of stereotactic radiosurgery (SRS) in the management of progressive or newly diagnosed small-volume oligodendrogliomas. Tumor control, survival, and complications were assessed in patients with oligodendroglioma who underwent Gamma Knife radiosurgery as a primary or adjuvant procedure.

METHODS
The authors retrospectively reviewed 30 patients with oligodendrogloma (12 Grade II and 18 Grade III) who underwent SRS between 1992 and June 2006 at the University of Pittsburgh. The median patient age was 43.2 years (range 10.8-75.4 years). Twenty-four patients had previously undergone resection of the tumor, whereas tumors in 6 were diagnosed based on biopsy findings. The SRS was performed in 25 patients who had imaging-defined tumor progression despite prior fractionated radiation (22 patients) and/or chemotherapy (20 patients). The median target volume was 15.4 cm(3) (range 0.07-48.7 cm(3)) and the median margin dose was 14.5 Gy (range 11-20 Gy).

RESULTS
At an average of 39.2 months of follow-up (range 12-133 months), 17 patients were dead and 13 were living. The overall survival rates from diagnosis to 5 and 10 years were 90.9 and 68.2%, respectively, for Grade II and 52.1% at 5 years and 26.1% at 10 years for Grade III. Factors associated with an improved progression-free survival included lower tumor grade and smaller tumor volume. In 13 patients who had loss of heterozygosity testing, patients with 1p19q loss of heterozygosity had a significantly improved survival after diagnosis (p = 0.04).

CONCLUSIONS
The SRS modality is a minimally invasive additional option for patients with residual or recurrent oligodendrogliomas. It may also be considered as an alternative to initial resection in small-volume tumors located in the cortical brain region.
The role of the Gamma Knife in the management of cerebral astrocytomas.
Szeifert GT, Prasad D, Kamyrio T, Steiner M, Steiner LE.

Source
National Institute of Neurosurgery and Department of Neurological Surgery, Semmelweis University, Budapest, Hungary. gyorgyszeifert@yahoo.com

Abstract
The aim of this study was to assess the role of Gamma Knife radiosurgery in the complex management of cerebral astrocytomas. Out of a series with more than 1,000 brain tumor cases treated at the Lars Leksell Center for Gamma Knife Surgery, UVA, 74 astrocytomas were selected for the present review. The tumor either disappeared or decreased in 60% of grade 1 astrocytomas (n = 15), and 71% tumor control was achieved in grade 2 astrocytomas (n = 17) following radiosurgery. In the high-grade glioma group (grades 3 and 4; n = 42) median survival time was 14 (range 2-58) months, and 25% of the patients were alive at 5 years after the treatment. The best results were presented by the subgroup wherein previous craniotomy and debulking of the tumor were followed by radiosurgery (n = 7) with a median survival period of 24 (range 2-53) months. Results of the present analysis suggest that stereotactic radiosurgery represents an alternative or supplementary treatment modality to conventional surgery in small-volume low-grade astrocytomas especially in deep-seated critical locations. There is also evidence for the beneficial effect of radiosurgery on the survival of patients with high-grade gliomas; however, the limitations of a focused irradiation technique on a malignant infiltrative process are obvious.

Gamma knife surgery for focal brainstem gliomas.
Yen CP, Sheehan J, Steiner M, Patterson G, Steiner L.

Lars Leksell Center for Gamma Surgery, Department of Neurological Surgery, University of Virginia Health System, Charlottesville, Virginia 22908, USA.

OBJECT
Focal tumors, a distinct subgroup of which is composed of brainstem gliomas, may have an indolent clinical course. In the past, their management involved monitoring of open-ended imaging studies and shunt placement if cerebrospinal fluid diversion was required. Nonetheless, their treatment remains a significant challenge for neurosurgeons. Gamma Knife surgery (GKS) has recently been tried as an
alternative to surgical extirpation. In the present study the authors assess clinical and imaging results in 20 patients who harbored focal brainstem gliomas treated with GKS between 1990 and 2001.

METHODS
There were 10 male and 10 female patients with a mean age of 19.1 years. Sixteen tumors were located in the midbrain, three in the pons, and one in the medulla oblongata. The mean tumor volume at the time of GKS was 2.5 cm³. In 10 cases a tumor specimen was obtained either by open surgery or stereotactic biopsy, securing the diagnosis of pilocytic astrocytoma in five patients and nonpilocytic astrocytoma in five others. In the remaining 10 cases, the diagnosis was based on clinical and neuroimaging findings. The prescription Gamma Knife dose varied between 10 and 18 Gy, except in three patients who were receiving a boost to a site in which external-beam radiation was previously delivered. An average of four isocenters were utilized per GKS. Patients were followed up for a mean of 78.0 months. The tumors disappeared in four patients and shrank in 12 patients. Of these patients, one experienced transitory extrapyramidal symptoms and fluctuating impairment of consciousness (from somnolence to coma) for 6 months. Another patient whose tumor disappeared 3 years following GKS died of stroke 8 years postoperatively. The rest of the patients either remained stable or improved clinically. Tumor progression occurred in four patients; of these four, one patient developed hydrocephalus requiring a ventriculoperitoneal shunt, two showed neurological deterioration, and one 4-year-old boy died of tumor progression.

CONCLUSIONS
Gamma Knife surgery may be an effective primary treatment or adjunct to open surgery for focal brainstem gliomas.

Wang LW, Shiau CY, Chung WY, Wu HM, Guo WY, Liu KD, Ho DM, Wong TT, Pan DH.
Cancer Center, Taipei Veterans General Hospital, Taiwan, Republic of China. lwang@vghtpe.gov.tw

OBJECT
The authors report the long-term treatment results of Gamma Knife surgery (GKS) for patients with low-grade astrocytomas who underwent surgery at a single institution.

METHODS
A series of 21 patients (median age 20 years) with 25 intracranial low-grade astrocytomas (World Health Organization Grades I and II) were treated with GKS between 1993 and 2003. Among them, four underwent GKS as a primary treatment. Two underwent GKS as a treatment boost after radiotherapy. In the other 15 patients, GKS was performed as an adjuvant or salvage treatment for residual/recurrent
tumors after the patients had undergone craniotomy. Tumor volumes ranged from 0.2 to 13.3 ml (median 2.4 ml). Prescription margin doses ranged from 8 to 18 Gy (median 14.5 Gy). Radiation volumes were 1.3 to 21.6 ml (median 3.6 ml). Patients underwent regular follow up, with neurological evaluation and magnetic resonance imaging studies obtained at 6-month intervals. One patient was lost to follow-up. The clinical follow-up time was 5 to 144 months (median 67 months). Complete tumor remission was seen in three patients. **The 10-year progression-free patient survival rate after GKS was 65%.** Tumor progression was found in six patients of whom five received further salvage treatment. All the tumor progression occurred within the GKS-treated volumes. Mild-to-moderate adverse radiation effects (AREs) were found in eight patients. Both of the patients who had undergone GKS as a treatment boost after radiotherapy developed AREs, but with good shrinkage of tumors.

**CONCLUSIONS**
Gamma Knife surgery provides durable long-term local tumor control with acceptable toxicity for some patients with highly selected low-grade astrocytomas.

**Neurosurg Focus. 2006 Apr 15;20(4):E17.**
Gamma knife surgery for glioblastoma multiforme.
Crowley RW, Pouratian N, Sheehan JP.

Department of Neurological Surgery, University of Virginia Health System, Charlottesville, Virginia 22908-0212, USA.

**Abstract**
Despite the implementation of increasingly aggressive surgery, chemotherapy, and fractionated radiotherapy for the treatment of glioblastoma multiforme (GBM), most therapeutic regimens have resulted in only modest improvements in patient survival. Gamma knife surgery (GKS) has become an indispensable tool in the primary and adjuvant management of many intracranial pathologies, including meningiomas, pituitary tumors, and arteriovenous malformations. Although it would seem that radiosurgical techniques, which produce steep radiation dose fall-off around the target, would not be well suited to treat these infiltrative lesions, a limited number of institutional series suggest that GKS might provide a survival benefit when used as part of the comprehensive management of GBM. This may largely be attributed to the observation that tumors typically recur within a 2-cm margin of the tumor resection cavity. Despite these encouraging results, enthusiasm for radiosurgery as a primary treatment for GBM is significantly tempered by the failure of the only randomized trial that has been conducted to yield any benefit for patients with GBM who were treated with radiosurgery. In this paper, the authors review the pathophysiological mechanisms of GKS and its applications for GBM management.
The role of Gamma Knife Radiosurgery in the management of unresectable gross disease or gross residual disease after surgery in ependymoma.

Department of Radiation Oncology, Indiana University Medical Center, 535 Barnhill Drive, RT 041, Indianapolis, IN 46202, USA.

PURPOSE/OBJECTIVE
To evaluate the efficacy and the toxicity of Gamma Knife (GK)-based stereotactic radiosurgery (SRS) in the management of gross disease in ependymoma.

MATERIALS AND METHODS
Eight patients with 13 ependymomas were treated with GK-based SRS in our institution for gross disease. Five patients were treated for recurrent disease that developed after surgery and external beam radiotherapy (EBRT), two received SRS to the gross disease after surgery and EBRT, and one received SRS alone (in a 1.3 year old child). Median EBRT dose was 54.4 Gy (range 50-55.8 Gy). Median SRS dose was 14 Gy (range 12-20 Gy). Seven of eight (87.5%) patients had SRS to a single lesion and one of eight (12.5%) patients had treatment to six tumors in three different sessions.

RESULTS
The median follow up was 30.2 months (range 8-65.4 months). Out of the eight patients treated with SRS, six (75%) were alive, four (50%) were alive with no recurrence, two (25%) were alive with recurrence, and two (25%) died of recurrent disease. Both patients treated with SRS as a boost were alive and without recurrence. Out of the five patients who received SRS as salvage treatment, three (60%) were alive, two (40%) were alive without recurrence, two (40%) developed distant failure, and three (60%) had in-field control. Two patients who received SRS to their brainstem lesions developed symptoms related to radionecrosis and were successfully treated with steroid with good control of symptoms.

CONCLUSIONS
GK-based SRS appears to be a feasible and safe treatment modality for patients with ependymoma with unresectable gross disease or gross residual disease after surgery. SRS provides reasonable local control but out-of-field tumor progression remains an issue. For patients who receive SRS as a boost, the local control appears to be excellent.
Gamma knife surgery for low-grade gliomas.
Heppner PA, Sheehan JP, Steiner LE.

The Lars Leksell Gamma Knife Center, Department of Neurological Surgery, University of Virginia, Charlottesville, Virginia, USA.

OBJECT
Data regarding the long-term efficacy of Gamma knife surgery on a large series of patients with low-grade gliomas is lacking. We aimed to review the outcome of patients with low-grade gliomas undergoing Gamma knife surgery at the Lars Leksell Gamma Knife Center at the University of Virginia to clarify its role in the management of these lesions.

METHODS
A retrospective review of 49 patients treated between 1989 and 2003 was conducted. The median follow up was 63 months. Gamma knife surgery was generally performed for tumors in eloquent brain, residual tumor post-surgery or for late progression after surgery.

RESULTS
Median clinical progression free survival was 44 months and median radiological progression free survival was 37 months. Five-year radiological progression free survival was 37% while clinical progression free survival was 41%. Mortality due to tumor progression occurred in 7 patients (14%). Complete radiological remission was seen in 14 patients (29%). Complications due to Gamma surgery were seen in 4 patients (8%). Of these, two resolved without sequelae, one required surgery for neurological decline and associated radiation induced changes, and one patient suffered a permanent neurological deficit from treatment.

CONCLUSION
Gamma knife radiosurgery is a safe treatment for low-grade gliomas and may be considered in patients with residual or recurrent disease.

Adjuvant gamma knife stereotactic radiosurgery at the time of tumor progression potentially improves survival for patients with glioblastoma multiforme.

Source
Abstract

OBJECTIVE
Gamma knife stereotactic radiosurgery (GK-SRS) is a safe and noninvasive treatment used as adjuvant therapy for patients with glioblastoma multiforme (GBM). Several studies have yielded conflicting results in the effectiveness of radiosurgery in GBM. This study is a retrospective review of our institutional experience with GK-SRS adjuvant therapy in the treatment of GBM.

METHODS
From October 1998 to January 2003, 51 consecutive patients were treated with GK-SRS as an "upfront" adjuvant therapy after surgery or at the time of tumor progression at Northwestern Memorial Hospital. Survival analysis was performed using the Kaplan-Meier actuarial method. Univariate and multivariate analyses of patient characteristics and treatment variables were performed.

RESULTS
Treatment with adjuvant GK-SRS yielded a median overall survival of 14.3 months for our cohort. Survival rate of the cohort was 68% at 12 months, 30% at 24 months, and 24% at 36 months. Karnofsky performance score greater than 90 and adjuvant chemotherapy were associated with increased survival on multivariate analysis. Adjuvant GK-SRS performed at tumor progression seems to increase median survival to 16.7 months compared with 10 months when performed after the time of initial tumor resection. Median survival rates by recursive partitioning analysis class breakdown in our cohort are greater than those predicted by other studies.

CONCLUSION
GK-SRS is a relatively safe and noninvasive procedure that conferred an improvement in overall survival of GBM patients in our retrospective study. Particularly, GK-SRS may improve overall survival when performed at the time of tumor progression.

The American Society for Therapeutic Radiology and Oncology (ASTRO) evidence-based review of the role of radiosurgery for malignant glioma.
Tsao MN, Mehta MP, Whelan TJ, Morris DE, Hayman JA, Flickinger JC, Mills M, Rogers CL, Souhami L.
The American Society for Therapeutic Radiology and Oncology, Fairfax, VA 22033, USA.

PURPOSE
To systematically review the evidence for the use of stereotactic radiosurgery or stereotactic fractionated radiation therapy in adult patients with malignant glioma.
METHODS
Key clinical questions to be addressed in this evidence-based review were identified. Outcomes considered were overall survival, quality of life or symptom control, brain tumor control or response and toxicity. MEDLINE (1990-2004 June Week 2), CANCERLIT (1990-2003), CINAHL (1990-2004 June Week 2), EMBASE (1990-2004 Week 25), and the Cochrane library (2004 issue 2) databases were searched using OVID. In addition, the Physician Data Query clinical trials database, the proceedings of the American Society of Clinical Oncology (1997-2004), ASTRO (1997-2004), and the European Society of Therapeutic Radiology and Oncology (ESTRO) (1997-2003) were searched. Data from the literature search were reviewed and tabulated. This process included an assessment of the level of evidence.

RESULTS
For patients with newly diagnosed malignant glioma, radiosurgery as boost therapy with conventional external beam radiation was examined in one randomized trial, five prospective cohort studies, and seven retrospective series. There is Level I evidence that the use of radiosurgery boost followed by external beam radiotherapy and carmustine (BCNU) does not confer benefit with respect to overall survival, quality of life, or patterns of failure as compared with external beam radiotherapy and BCNU. There is Level I-III evidence of toxicity associated with radiosurgery boost as compared with external beam radiotherapy alone. The results of the prospective and retrospective studies may be influenced by selection bias. Radiosurgery used as salvage for recurrent or progressive malignant glioma after conventional external beam radiotherapy failure was reported in zero randomized trials, three prospective cohort studies, and five retrospective series. The available data are sparse and insufficient to make absolute recommendations. Stereotactic fractionated radiation therapy has been reported as boost therapy with external beam radiotherapy for patients with newly diagnosed malignant glioma in only three prospective studies. As primary therapy alone without conventional external beam radiotherapy for newly diagnosed malignant glioma patients, stereotactic fractionated radiation therapy has been reported in only one prospective study. There were only three prospective series and two retrospective studies reported for patients with recurrent or progressive malignant glioma.

CONCLUSIONS
For patients with malignant glioma, there is Level I-III evidence that the use of radiosurgery boost followed by external beam radiotherapy and BCNU does not confer benefit in terms of overall survival, local brain control, or quality of life as compared with external beam radiotherapy and BCNU. The use of radiosurgery boost is associated with increased toxicity. For patients with malignant glioma, there is insufficient evidence regarding the benefits/harms of using radiosurgery at the time progression or recurrence. There is also insufficient evidence regarding the benefits/harms in the use of stereotactic fractionated radiation therapy for patients with newly diagnosed or progressive/recurrent malignant glioma.
The role of stereotactic radiosurgery for low-grade astrocytomas.
Hadjipanayis CG, Kondziolka D, Flickinger JC, Lunsford LD.

Source
Department of Neurological Surgery, Center for Image-Guided Neurosurgery, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania 15213, USA. Costas111@pol.net

Abstract
OBJECT
This study was conducted to examine the role of radiosurgery in the management of patients with recurrent or unresectable low-grade astrocytomas.

METHODS
During a 13-year interval, 49 patients underwent stereotactic radiosurgery as part of multimodal treatment of their recurrent or unresectable low-grade astrocytomas. Thirty-seven of these patients (median age 14 years) harbored pilocytic astrocytomas and 12 patients harbored World Health Organization (WHO) Grade II fibrillary astrocytomas (median age 25 years). Tumors involved the brainstem in 22 cases, cerebellum in four, thalamus in six, temporal lobe in five, frontal lobe in four, and parietal lobe in three, as well as the hypothalamus, corpus callosum, insular cortex, optic tract, and third ventricle in one patient each. Each diagnosis was confirmed with the aid of stereotactic biopsy sampling in 17 patients, open biopsy sampling in five, partial resection in 13, and near-total resection in 14. Multimodal treatment included fractionated radiotherapy in 14 patients, stereotactic intracavitary irradiation in five, chemotherapy in two, cyst drainage in eight, ventriculoperitoneal shunt placement in five, and additional cytoreductive surgery in five. Tumor volumes ranged from 0.42 to 45.1 cm3. The median radiosurgical dose to the tumor margin was 15 Gy (range 9.6-22.5 Gy). After radiosurgery, serial neuroimaging demonstrated complete tumor resolution in 11 patients, reduced tumor volume in 12, stable tumor volume in 10, and delayed tumor progression in 16. No procedure-related death was encountered. Forty-five of 49 patients are alive at a median follow-up period of 32 months after radiosurgery and 63 months after diagnosis. Sixteen patients participated in follow-up review for more than 60 months. Three patients died of local tumor progression.

CONCLUSIONS
Stereotactic radiosurgery is a potential alternative or adjunctive intervention in the management of selected patients with pilocytic or WHO Grade II fibrillary astrocytomas, usually performed for small-volume tumors in an attempt to avoid larger-field fractionated radiotherapy.
In this paper, we studied factors related to long-term survival after gamma knife radiosurgery (GKS) for primary and metastatic brain tumors. We examined all cases of brain metastases and malignant glioma treated with GKS between September 1994 and December 1998. All patients with survival exceeding 2 years were studied retrospectively using prospectively acquired data. A total of 22 patients, with an average age of 56, were identified, which accounts for 11% of the total patients treated during this time interval. Seventeen of 22 are still alive with a mean follow-up of 48 months. Sixteen patients had metastastic tumors, whereas 6 had a malignant glioma. Thirteen of 15 patients with metastases had a controlled primary site, and the other 2 patients did not have a primary site identified. These 2 patients were among the 3 that died during the follow-up period. Fourteen patients developed symptomatic radiation necrosis by MRI criteria with 4 confirmed by biopsy. Quality-of-life factors were assessed in 20 of 22 patients using a modified Spitzer scale, which showed a high level of functioning in all of the long-term survivors (mean score 8.65 of 10), and only 1 patient had a Karnofsky Performance Score of less than 70. We conclude that radiosurgery provides a noninvasive and effective way of controlling brain tumors, while preserving quality of life.
extended area of MET accumulation on PET imaging (MET area), the gadolinium (Gd) enhanced area on T1 weighted images (Gd area), and the abnormal high signal intensity area on T2 weighted images (T2-high area) were assessed.

RESULTS

The MET area was larger than the Gd area and included the entire Gd area. The discrepancy in volume between the MET and Gd areas became greater with increasing tumour diameter. On average, 58.6% of the MET area was located within the Gd area, 90.1% within 10 mm outside the Gd area, 98.1% within 20 mm, and 99.8% within 30 mm. A newly developed Gd area had emerged in five of the 10 cases up to the time of study. In three of the five cases this was in the MET area even after complete surgical resection of the Gd area on the initial MRI; in the remaining two it originated in the residual Gd area after surgery. In all cases, the T2-high area was larger than the MET area. The MET area extended partly beyond the T2-high area in nine cases, and was completely within it in one.

CONCLUSIONS

Glioblastoma multiforme cells may extend over the Gd area and more widely with increasing tumour size on Gd-MRI. The T2-high area includes the greater part of the tumour but not its entire area. The methods reported may be useful in planning surgical resection, biopsy, or radiosurgery.

The role of gamma knife radiosurgery in the treatment of primary and metastatic brain tumors.
Gerona M, Nicolato A, Foroni R.

Department of Neurosurgery, University Hospital, Piazzale Stefani 1, 37126 Verona, Italy.
massimo.gerona@univr.it

Abstract
With the widespread diffusion of stereotactic radiosurgical procedures, GKR treatments have gained considerable momentum as a major therapeutic option for patients harboring primary or metastatic brain tumors. Present results in high grade gliomas indicate a potential palliative role of this technique. The overall low radiosensitivity of these oncotypes and their infiltrative nature-with the resulting problems in properly defining the tumor target-are still a major obstacle to further development of the approach. In this regard, useful contributions are expected from advances in molecular neurobiology and functional neuroimaging as shown by preliminary investigations with MR spectroscopy. Surgery maintains a dominant role in the therapeutic armamentarium for low grade gliomas. However, in unfavorable cases (unresectable tumors, recurrences), GKR seems to be an effective alternative to conventional radiochemotherapy. In grade 2 astrocytomas and specifically in grade 1 pilocytic forms, short-to-mid-term reported studies have documented encouraging 70 to 93% local
**tumor control rates, with minimal cerebral toxicity.** Finally, during the last decade, GKR has become a primary treatment choice for patients harboring small-to-medium-size brain metastases, with reasonable life expectancy and no impending intracranial hypertension. Focal tumor responses are consistently elevated, even in the most radioresistant oncotypes (melanoma, renal carcinoma); median and actuarial survival rates are far better than with conventional radiation treatments and are comparable to those observed in accurately selected surgical-radiation series.

**J Neurosurg. 2002 Dec;97(5 Suppl):677-80.**

Gamma knife radiosurgery for pilocytic astrocytomas.
Boëthius J, Ulfarsson E, Rähn T, Lippitz B.

**Source**
Department of Neurosurgery, Karolinska Hospital, Stockholm, Sweden. jboethius@yahoo.com

**Abstract**

**OBJECT**
The authors report on the follow-up studies in patients treated at the Karolinska Hospital to evaluate the efficacy of gamma knife radiosurgery (GKS) for pilocytic astrocytoma.

**METHODS**
Twelve male and seven female patients were treated (mean age 10.6 years [range 2-60 years]). Sixteen of these patients were children in whom GKS was performed to treat residual tumor after surgery. Most tumors were treated with a prescription dose of 10 to 12 Gy (range 9-20 Gy). The corresponding maximum dose varied between 22 and 30 Gy (range 10-50 Gy). **The median clinical follow-up time was 7 years and mean clinical follow-up time 8.5 years. Median radiological follow-up time was 4.7 years and the mean radiological follow-up time was 5.9 years. Tumor control was achieved in all patients.** In 85% of the cases a moderate tumor volume reduction was observed after GKS. This result occurred despite the low prescription dose administered. The radiological follow-up studies showed adverse radiation effects in 25% of patients with increasing contrast enhancement and some edema. These effects generally appeared within 7 months and resolved later. Cyst development occurred in two patients, which may have been treatment related.

**CONCLUSIONS**

It appears that small pilocytic astrocytomas may be treated with low-prescription-dose GKS, resulting in satisfactory clinical outcomes and only minor side effects. There were a certain number of radiologically demonstrated side effects that appeared relatively early but subsequently resolved. This study should be regarded as a preliminary one because the number of patients is small and the follow-up period is short compared with the natural time course of the disease.
**Acta Neurochir Suppl. 2002;84:85-90.**

Gamma Knife radiosurgery of brainstem gliomas.
Fuchs I, Kreil W, Sutter B, Papaethymiou G, Pendl G.

Department of Neurosurgery, Karl-Franzens University, Graz, Austria.

**Abstract**

From August 1992 until December 1999 Gamma Knife radiosurgery (GKRS) was applied to 21 patients (male to female ratio 14:7) with brainstem gliomas. Patient's median age was 23 years (8-56 years). All tumours were histologically confirmed by biopsy or open surgery: 12 low-grade gliomas and 9 malignant growths. Two lesions were located primarily in the medulla, 12 in the pons and 7 in the midbrain. A median dose of 12 Gy (9-20 Gy) was applied to the tumour margin by the median isodose of 45%. Prior to radiosurgery 4 patients were treated by conventional radiotherapy, 1 had radiotherapy and chemotherapy, 1 patient underwent chemotherapy, and 1 patient was shunted due to hydrocephalus.

Neuroimaging controls (MR, CT) were obtained from 19 patients. The median interval between radiosurgery and the last neuroimaging control was 11.8 months (1-74 months). Neuroimaging depicted tumour progression in 2 patients, stable disease in 10 patients and regression in 3 cases. Follow-up periods ranged between 3 and 99 months (median 29 months). The neurological state improved in 5 patients. Microsurgical cyst fenestration was performed in 1 patient after GKRS, shunting procedure was necessary for 2 patients. Nine patients died unrelated to radiosurgery within 3 to 45 months (median 20.7 months). GKRS is an effective treatment modality for brainstem gliomas with satisfying tumour control and functional outcome.

**J Neurosurg. 2002 Jul;97(1):56-64.**

Stereotactic radiosurgery for pilocytic astrocytomas when multimodal therapy is necessary.
Hadjipanayis CG, Kondziolka D, Gardner P, Niranjan A, Dagam S, Flickinger JC, Lunsford LD.

**Source**

Department of Neurological Surgery, University of Pittsburgh Medical Center, Pennsylvania 15213, USA.
Costas111@pol.net

**Abstract**

**OBJECT**

The goal of this study was to examine the role of stereotactic radiosurgery in the treatment of patients with recurrent or unresectable pilocytic astrocytomas.

**METHODS**

During a 13-year interval, 37 patients (median age 14 years) required multimodal treatment of recurrent or unresectable pilocytic astrocytomas. Tumors involved the brainstem in 18 patients,
cerebellum in three, thalamus in five, temporal lobe in four, and parietal lobe in two, as well as the hypothalamus, optic tract, corpus callosum, insular cortex, and third ventricle in one patient each. Diagnosis was confirmed with the aid of stereotactic biopsy in 12 patients, open biopsy in five, partial resection in eight, and near-total resection in 12. Multimodal treatment included fractionated radiation therapy in 10 patients, stereotactic intracavitary irradiation of tumor in four, chemotherapy in two, cyst drainage in six, ventriculoperitoneal shunt placement in three, and additional cytoreductive surgery in four. Tumor volumes varied from 0.42 to 25 cm³. The median radiosurgical dose to the tumor margin was 15 Gy (range 9.6-22.5 Gy). After radiosurgery, serial imaging demonstrated complete tumor resolution in 10 patients, reduced tumor volume in eight, stable tumor volume in seven, and delayed tumor progression in 12. No procedure-related death was encountered. Thirty-three (89%) of 37 patients are alive at a median follow-up period of 28 months after radiosurgery and 59 months after diagnosis. Eight patients participated in follow-up review for more than 60 months. Three patients died of local tumor progression.

CONCLUSIONS
Stereotactic radiosurgery is a valuable adjunctive strategy in the management of recurrent or unresectable pilocytic astrocytomas. Despite the favorable histological characteristics and prognosis usually associated with this neoplasm, an adverse location, recurrence, or progression of this disease requires alternative therapeutic approaches such as radiosurgery.

Gamma knife stereotactic radiosurgery for patients with glioblastoma multiforme.
Nwokedi EC, DiBiase SJ, Jabbour S, Herman J, Amin P, Chin LS.
Department of Radiation Oncology, University of Maryland School of Medicine, 22 South Greene Street, Baltimore, MD 21201, USA.

OBJECTIVE
Stereotactic radiosurgery (SRS) has become an effective therapeutic modality for the treatment of patients with glioblastoma multiforme (GBM). This retrospective review evaluates the impact of SRS delivered on a gamma knife (GK) unit as an adjuvant therapy in the management of patients with GBM.

METHODS
Between August 1993 and December 1998, 82 patients with pathologically confirmed GBM received external beam radiotherapy (EBRT) at the University of Maryland Medical Center. Of these 82 patients, 64 with a minimum follow-up duration of at least 1 month are the focus of this analysis. Of the 64 assessable patients, 33 patients were treated with EBRT alone (Group 1), and 31 patients received both EBRT plus a GK-SRS boost (Group 2). GK-SRS was administered to most patients within 6 weeks of the completion of EBRT. The median EBRT dose was 59.7 Gy (range, 28-
070.2 Gy), and the median GK-SRS dose to the prescription volume was 17.1 Gy (range, 10-28 Gy). The median age of the study population was 50.4 years, and the median pretreatment Karnofsky performance status was 80. Patient-, tumor-, and treatment-related variables were analyzed by Cox regression analysis, and survival curves were generated by the Kaplan-Meier product limit.

RESULTS
Median overall survival for the entire cohort was 16 months, and the actuarial survival rate at 1, 2, and 3 years were 67, 40, and 26%, respectively. When comparing age, Karnofsky performance status, extent of resection, and tumor volume, no statistical differences were discovered between Group 1 versus Group 2. When comparing the overall survival of Group 1 versus Group 2, the median survival was 13 months versus 25 months, respectively (P = 0.034). Age, Karnofsky performance status, and the addition of GK-SRS were all found to be significant predictors of overall survival via Cox regression analysis. No acute Grade 3 or Grade 4 toxicity was encountered.

CONCLUSION
The addition of a GK-SRS boost in conjunction with surgery and EBRT significantly improved the overall survival time in this retrospective series of patients with GBM. A prospective, randomized validation of the benefit of SRS awaits the results of the recently completed Radiation Therapy Oncology Group's trial RTOG 93-05.

Gamma knife radiosurgery for low-grade astrocytomas: results of long-term follow up.
Kida Y, Kobayashi T, Mori Y.

Department of Neurosurgery, Komaki City Hospital, Japan.

OBJECT
The purpose of this paper is to report the long-term results of gamma knife radiosurgery (GKS) for low-grade astrocytomas.

METHODS
Fifty-one patients with low-grade astrocytomas treated with GKS and followed for more than 24 months are reported. Of the 51 patients, 12 harbored Grade I astrocytomas in and around the visual pathways and hypothalamus. The remaining 39 harbored Grade II astrocytomas. The mean patient age at time of GKS was 9.8 years for patient with Grade I and 30.9 years for those with Grade II astrocytomas. The mean tumor diameter was 25.4 mm for Grade I and 23.7 mm for Grade II tumors. The mean margin dose was 12.5 Gy for Grade I and 15.7 Gy for Grade II tumors. In the mean follow-up period of 27.6 months, both Grade I and Grade II astrocytomas responded well to GKS. Grade I astrocytomas had a response rate of 50% and a control rate of 91.7%. Grade II astrocytomas had a 46.2% response rate and an 87.2% control rate. Statistical analyses
concerning the efficacy and related factors showed a significantly better response for patients 10 years of age or older with Grade I and those with a follow-up period of more than 24 months. Complications included radiation-induced edema in 18 (35.3%) of 51 cases, cyst formation or enlargement in five (9.8%), and transient tumor enlargement in three (5.9%).

CONCLUSIONS
Radiosurgery can play an important role in the treatment of low-grade astrocytomas, and complete cure of these tumors is expected in at least some of the cases.

Adjuvant stereotactic radiosurgery for anaplastic ependymoma.
Jawahar A, Kondziolka D, Flickinger JC, Lunsford LD.

Source
Departments of Neurological Surgery, Radiation Oncology and Center for Image Guided Neurosurgery, University of Pittsburgh Medical Center, PA 15213-2582, USA. ajawahar@neuronet.pitt.edu

Abstract
OBJECT
The purpose of this retrospective study is to evaluate the role of stereotactic radiosurgery using the Gamma Knife as an adjuvant to other modalities used in the treatment of malignant ependymomas of both children and adults and to assess its efficacy in terms of tumor control and overall survival.

METHOD
Between 1987 and 1998, 22 patients in the age range of 1.5-65 years (mean age 22.3) with progressive anaplastic ependymoma were treated by stereotactic radiosurgery using the 201 source Co-60 Leksell Gamma Knife at the University of Pittsburgh. The irradiated tumor volume varied from 0.84 to 36.8 cm(3) (mean 13.7). The median dose delivered to the tumor margin was 16.1 Gy (range 10-20), and the mean maximal dose was 32.2 Gy (range 20-40). The disease-free survival, the tumor control rate and the overall survival were recorded to evaluate the efficacy of radiosurgery. The median follow-up from radiosurgery was 21 months (range 4-84).

RESULTS
Median survival after radiosurgery was 2.2 years (46.6 +/- 12.1% 5-year actuarial). Median survival from the initial diagnosis was 10.1 years (50.3 +/- 12.5% at 5 years, 37.7 +/- 14.4% at 10 years). Reduction or stabilization of the treated tumor was seen in 16 out of 22 (68%) patients. Forty-one percent of the patients eventually developed delayed distant cerebral recurrence outside the treated volume. The 5-year actuarial rates for local control and cranial control at any location were 62.3 +/- 13.6% and 32.4 +/- 10.8%, respectively. No complication occurred as a side effect of radiosurgery.
CONCLUSION
For patients with locally recurrent or progressive anaplastic ependymomas, Gamma Knife stereotactic radiosurgery proved to be safe and effective as a salvage adjuvant therapy to achieve local tumor control and improve survival.

Gamma knife for glioma: selection factors and survival.
Department of Radiation Oncology, University of California, San Francisco 94143, USA.

PURPOSE
To determine factors associated with survival differences in patients treated with radiosurgery for glioma.

METHODS AND MATERIALS
We analyzed 189 patients treated with Gamma Knife radiosurgery for primary or recurrent glioma World Health Organization (WHO) Grades 1-4.

RESULTS
The median minimum tumor dose was 16 Gy (8-30 Gy) and the median tumor volume was 5.9 cc (1.3-52 cc). Brachytherapy selection criteria were satisfied in 65% of patients. Median follow-up of all surviving patients was 65 weeks after radiosurgery. For primary glioblastoma patients, median survival from the date of pathologic diagnosis was 86 weeks if brachytherapy criteria were satisfied and 40 weeks if they were not ($p = 0.01$), indicating that selection factors strongly influence survival. Multivariate analysis showed that increased survival was associated with five variables: lower pathologic grade, younger age, increased Karnofsky performance status (KPS), smaller tumor volume, and unifocal tumor. Survival was not found to be significantly related to radiosurgical technical parameters (dose, number of isocenters, prescription isodose percent, inhomogeneity) or extent of preradiosurgery surgery. We developed a hazard ratio model that is independent of the technical details of radiosurgery and applied it to reported radiosurgery and brachytherapy series, demonstrating a significant correlation between survival and hazard ratio.

CONCLUSIONS
Survival after radiosurgery for glioma is strongly related to five selection variables. Much of the variation in survival reported in previous series can be attributed to differences in distributions of these variables. These variables should be considered in selecting patients for radiosurgery and in the design of future studies.
Early outcomes after stereotactic radiosurgery for growing pilocytic astrocytomas in children.
Somaza SC, Kondziolka D, Lunsford LD, Flickinger JC, Bissonette DJ, Albright AL.

Source
Department of Neurosurgery, University of Pittsburgh Medical Center, Pa., USA.

Abstract
To examine the role of stereotactic radiosurgery in the adjuvant management of children with growing and unresectable deep-seated pilocytic astrocytomas, we reviewed our experience in 9 patients. The tumors were located in the dorsolateral pons (n = 2), midbrain (n = 1, cerebellar peduncle (n = 2), thalamus (n = 1), temporal lobe (n = 1), hypothalamus (n = 1), and caudate nucleus (n = 1). The mean tumor diameter was 16 mm (range, 11-25 mm). Seven patients had prior partial tumor resection, and 2 had a stereotactic biopsy. Two patients had failed fractionated radiotherapy and 7 were considered at risk for adverse radiation effects because of their age. The mean dose to the tumor margin at radiosurgery was 15 Gy (range, 12-18). During mean follow-up of 19 months (range 13-41 months), there was a marked decrease in tumor size in 5 patients; 4 patients had no further growth. No early or delayed morbidity was associated with radiosurgery. Gamma knife radiosurgery proved a safe and effective therapeutic tool in the management of children with deep, small volume pilocytic astrocytomas. Because this tumor often appears well-delineated on contrast-enhanced neuroimaging, we believe that conformal radiosurgical targeting accurately irradiates tumor cells. For small tumor volumes it can be used in place of fractionated larger-field radiotherapy. The ability to treat the tumor yet spare surrounding brain may reduce the surgical morbidity associated with attempted radical resection and the potential cognitive and endocrine disabilities associated with fractionated radiation therapy.
7. Arterio-venous malformations (AVM)

An arterio-venous malformation (AVM) in the brain is a vascular anomaly resulting in a direct connection (shunt) between arteries and veins. There is no capillary “filter” in an AVM. The absence of capillaries creates a lack of resistance and hence a short-cut for blood to pass directly from arteries to veins. The blood pressure is much higher in arteries than in veins. Without the capillary filter reducing the pressure, the veins are not prepared to sustain the arterial pressure and can burst which results in a bleeding within the brain potentially resulting in neurological deficits or even death. Other patients with AVMs of the brain may experience epileptic seizures even without a bleeding.

Hence, when possible, AVMs are removed to prevent a bleeding in the brain. The removal can be achieved through a classical neurosurgical operation under the microscope. As an alternative it is sometimes possible to reduce the volume of the AVM or its blood flow using an intravascular approach, through embolization, when the pathological arterio-venous shunts are occluded from within using highly selective catheters. Unfortunately only in exceptions the endovascular approach achieves a complete occlusion of the AVM.

An increasingly important alternative is the AVM treatment with Gamma Knife radiosurgery. So far more than 60,000 AVM therapies have been carried out using Gamma Knife radiosurgery and the results are well documented. The AVM is localised with both angiography and MRI and the treated with focal Gamma Knife radiation. The result is an irritation of the vessel wall that slowly occludes the pathological vessels of the AVM. This process takes 2-3 years. This occlusion generally prevents potential future bleedings and the patient is considered cured.

Selected Literature 2001-2012: Gamma Knife Radiosurgery for Arterio-Venous Malformations (AVM)

Radiosurgery for unruptured cerebral arteriovenous malformations: Long-term seizure outcome.
Yang SY, Gyu Kim D, Chung HT, Paek SH.

**Abstract**

**OBJECTIVE**
To date, seizures in relation to arteriovenous malformations (AVM) have been a secondary target of most studies. The insufficient evaluation, in conjunction with the lack of consistent seizure outcome assessment, has made it been difficult to draw conclusions about seizure outcome after radiosurgery for AVM. This study aimed to determine the effect of radiosurgery on seizure outcome depending on AVM obliteration and on the development of new seizure in patients with AVM.

METHODS
Between 1997 and 2006, 161 consecutive patients underwent radiosurgery for unruptured AVM and were retrospectively assessed with a mean follow-up of 89.8 months by their medical records, updated clinical information, and, when necessary, direct patient contact. Seizure outcome was assessed using the Engel seizure frequency scoring system.

RESULTS
Of the 86 patients with a history of seizure before radiosurgery, 76.7% (66/86) were seizure-free and 58.1% (50/86) were medication-free at the last follow-up visit. Of the patients who achieved AVM obliteration, 96.7% (58/60) were seizure-free while 30.8% (8/26) of those patients who did not achieve AVM obliteration were seizure-free (p = 0.001). The proportion of patients who were medication-free was 81.7% (49/60) of the patients with obliteration and 3.8% (1/26) of patients without obliteration (p < 0.001). Of the 75 patients with no history of seizure before radiosurgery, 10 had provoked seizures due to the direct and indirect radiosurgical influences after radiosurgery.

CONCLUSIONS
Although radiosurgery tends to cause seizures temporarily, the radiosurgery may improve seizure outcomes in patients with AVM-related seizures, especially in patients with AVM obliteration.

Quality of life after radiosurgery for cerebral arteriovenous malformation patients who present with seizure.
Yang SY, Paek SH, Kim DG, Chung HT.
Department of Neurosurgery, Dongguk University Graduate School, Seoul Department of Neurosurgery, Seoul National University College of Medicine, Seoul, Korea.

BACKGROUND AND PURPOSE
This study assessed the quality of life (QOL) and employment status after radiosurgery for arteriovenous malformation (AVM) patients who presented with seizure.

METHODS
Between 1997 and 2006, 78 AVM patients who presented with seizure and received radiosurgery were assessed using serial imaging tests, clinical evaluations that included employment status, and a QOL survey. The QOL questionnaire was developed as a retrospective screening tool to estimate the present QOL and the patient’s self-rated relative changes (trend values) in QOL after radiosurgery. These results were correlated to one another using the Engel seizure frequency scoring system.

RESULTS:
The follow-up periods ranged from 48.0 to 151.0 months (mean, 92.5). The mean trend values and mean QOL scores in patients with seizure freedom or AVM obliteration were significantly greater than in patients without these outcomes (all P values < 0.05). Good radiosurgical outcomes were associated with attaining employment (all P values < 0.05). However, differences in employment status were not significant (P = 0.186) despite a higher proportion of patients who described their workplace activity as improved compared with their pre-radiosurgical activity at the last follow-up evaluation.

CONCLUSIONS:
Radiosurgery may improve QOL and employment status in AVM patients, especially patients who experience seizure freedom or AVM obliteration.


Departments of Neurological Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.

OBJECT
The authors conducted a study to define the long-term outcomes and risks of stereotactic radiosurgery (SRS) for pediatric arteriovenous malformations (AVMs).

METHODS
Between 1987 and 2006, the authors performed Gamma Knife surgery in 996 patients with brain AVMs; 135 patients were younger than 18 years of age. The median maximum diameter and target volumes were 2.0 cm (range 0.6-5.2 cm) and 2.5 cm(3) (range 0.1-17.5 cm(3)), respectively. The median margin dose was 20 Gy (range 15-25 Gy).

RESULTS
The actuarial rates of total obliteration documented by angiography or MR imaging at 71.3 months (range 6-264 months) were 45%, 64%, 67%, and 72% at 3, 4, 5, and 10 years,
respectively. The median time to complete angiographically documented obliteration was 48.9 months. Of 81 patients with 4 or more years of follow-up, 57 patients (70%) had total obliteration documented by angiography. Factors associated with a higher rate of documented AVM obliteration were smaller AVM target volume, smaller maximum diameter, and larger margin dose. In 8 patients (6%) a hemorrhage occurred during the latency interval, and 1 patient died. The rates of AVM hemorrhage after SRS were 0%, 1.6%, 2.4%, 5.5%, and 10.0% at 1, 2, 3, 5, and 10 years, respectively. The overall annual hemorrhage rate was 1.8%. Larger volume AVMs were associated with a significantly higher risk of hemorrhage after SRS. Permanent neurological deficits due to adverse radiation effects developed in 2 patients (1.5%) after SRS, and in 1 patient (0.7%) delayed cyst formation occurred.

CONCLUSIONS
Stereotactic radiosurgery is a gradually effective and relatively safe management option for pediatric patients in whom surgery is considered to pose excessive risks. Although hemorrhage after AVM obliteration did not occur in the present series, patients remain at risk during the latency interval until obliteration is complete. The best candidates for SRS are pediatric patients with smaller volume AVMs located in critical brain regions.

Neurosurgery. 2011 Dec 19. [Epub ahead of print]
Stereotactic Radiosurgery for Arteriovenous Malformations Located in Deep Critical Regions.
Nagy G, Major O, Rowe JG, Radatz MW, Hodgson TJ, Coley SC, Kemeny AA.

BACKGROUND
Radiosurgery is widely used to treat deep eloquent arteriovenous malformations (AVMs).

OBJECTIVE
To evaluate how anatomical location, AVM size and treatment parameters define outcome.

METHODS
Retrospective analysis of 356 thalamic/basal ganglia and 160 brainstem AVMs treated with gamma knife radiosurgery.

RESULTS
Median volume was 2cm (range 0.02-50) for supratentorial and 0.5cm (0.01-40) for brainstem AVMs; the marginal treatment doses were 17.5-25Gy. After single treatment, obliteration was achieved in 65% of the brainstem, in 69% of the supratentorial, and 40% of the perictetal AVMs.
Obliteration of lesions <4cm was better in the brainstem (70%) and in the supratentorium (80%), but not in the peritectal region (40%). Complications were rare (6-15%) and mild (≤MRS2). Rebleed rate increased with size, but was not higher than before treatment. AVMs >4cm in the brainstem were treated with unacceptable morbidity and low cure rate. Obliteration of large supratentorial AVMs was 65-47% with more complications ≥MRS3. Repeat radiosurgical treatment led to obliteration in 66% of the cases with minor morbidity.

CONCLUSION
Deep eloquent AVMs <4cm can be treated safely and effectively with radiosurgery.
Obliteration of peritectal AVMs is significantly lower after a single treatment. However, morbidity is low and repeat treatment leads to good obliteration. Radiosurgical treatment >4cm in the brainstem is not recommended. Supratentorial deep AVMs >8cm can be treated with radiosurgery with higher risk and lower obliteration rate. However, these lesions are difficult to treat with other treatment modalities and a 50% success rate makes radiosurgery a good alternative even in this challenging group.

A historical analysis of single-stage gamma knife radiosurgical treatment for large arteriovenous malformations: evolution and outcomes.
Nagy G, Rowe JG, Radatz MW, Hodgson TJ, Coley SC, Kemeny AA.
The National Centre for Stereotactic Radiosurgery, Royal Hallamshire Hospital, Sheffield, UK.
gnagydr@gmail.com

BACKGROUND
Large arteriovenous malformations (AVMs) remain challenging and difficult to treat, reflected by evolving strategies developed from simple radiosurgical plans, to encompass embolization and, recently, staged volume treatments. To establish a baseline for future practice, we reviewed our clinical experience.

METHOD:
The outcomes for 492 patients (564 treatments) with AVMs >10 cm(3) treated by single-stage radiosurgery were retrospectively analysed in terms of planning, previous embolization and size.

RESULTS
Twenty-eight percent of the patients presented with haemorrhage at a median age of 29 years (range: 2-75). From 1986 to 1993 (157 patients) plans were simplistic, based on angiography using a median of 2 isocentres and a marginal dose of 23 Gy covering 45-70% of the AVM (median volume 15.7 cm(3)). From 1994 to 2000 (225 patients) plans became more sophisticated, a median of 5 isocentres was used, covering 64-95% of the AVM (14.6 cm(3)), with a marginal dose of 21 Gy. Since 2000, MRI has been
used with angiography to plan for 182 patients. Median isocentres increased to 7 with similar coverage (62-94%) of the AVM (14.3 cm(3)) and marginal dose of 21 Gy. Twenty-seven percent, 30% and 52% of patients achieved obliteration at 4 years, respectively. The proportion of prior embolization increased from 9% to 44% during the study. Excluding the embolized patients, improvement in planning increased obliteration rates from 28% to 36% and finally 63%. Improving treatment plans did not significantly decrease the rate of persisting radiation-induced side effects (12-16.5%). Complication rate rose with increasing size. One hundred and twenty-three patients underwent a second radiosurgical treatment, with a 64% obliteration rate, and mild and rare complications (6%).

CONCLUSIONS
Better visualization of the nidus with multimodality imaging improved obliteration rates without changing morbidity. Our results support the view that prior embolization can make interpretation of the nidus more difficult, reducing obliteration rate. It will be important to see how results of staged volume radiosurgery compare with this historical material.

Department of Neurological Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213, USA.

OBJECT
The aim of this paper was to define the outcomes and risks of stereotactic radiosurgery (SRS) for Spetzler-Martin Grade I and II arteriovenous malformations (AVMs).

METHODS
Between 1987 and 2006, the authors performed Gamma Knife surgery in 996 patients with brain AVMs, including 217 patients with AVMs classified as Spetzler-Martin Grade I or II. The median maximum diameter and target volumes were 1.9 cm (range 0.5-3.8 cm) and 2.3 cm(3) (range 0.1-14.1 cm(3)), respectively. The median margin dose was 22 Gy (range 15-27 Gy).

RESULTS
Arteriovenous malformation obliteration was confirmed by MR imaging in 148 patients and by angiography in 100 patients with a median follow-up of 64 months (range 6-247 months). The actuarial rates of total obliteration determined by angiography or MR imaging after 1 SRS procedure were 58%, 87%, 90%, and 93% at 3, 4, 5, and 10 years, respectively. The median
time to complete MR imaging-determined obliteration was 30 months. Factors associated with higher AVM obliteration rates were smaller AVM target volume, smaller maximum diameter, and greater marginal dose. Thirteen patients (6%) suffered hemorrhages during the latency period, and 6 patients died. Cumulative rates of AVM hemorrhage 1, 2, 3, 5, and 10 years after SRS were 3.7%, 4.2%, 4.2%, 5.0%, and 6.1%, respectively. This corresponded to rates of annual bleeding risk of 3.7%, 0.3%, and 0.2% for Years 0-1, 1-5, and 5-10, respectively, after SRS. The presence of a coexisting aneurysm proximal to the AVM correlated with a significantly higher hemorrhage risk. Temporary symptomatic adverse radiation effects developed in 5 patients (2.3%) after SRS, and 2 patients (1%) developed delayed cysts.

CONCLUSIONS
Stereotactic radiosurgery is a gradually effective and relatively safe option for patients with smaller volume Spetzler-Martin Grade I or II AVMs who decline initial resection. Hemorrhage after obliteration did not occur in this series. Patients remain at risk for a bleeding event during the latency interval until obliteration occurs. Patients with aneurysms and an AVM warrant more aggressive surgical or endovascular treatment to reduce the risk of a hemorrhage in the latency period after SRS.

Stereotactic radiosurgery for arteriovenous malformations, Part 4: management of basal ganglia and thalamus arteriovenous malformations.
Kano H, Kondziolka D, Flickinger JC, Yang HC, Flannery TJ, Niranjan A, Novotny J Jr, Lunsford LD.
Department of Neurological Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213, USA.

OBJECT
The authors conducted a study to define the long-term outcomes and risks of stereotactic radiosurgery (SRS) for arteriovenous malformations (AVMs) of the basal ganglia and thalamus.

METHODS:
Between 1987 and 2006, the authors performed Gamma Knife surgery in 996 patients with brain AVMs; 56 patients had AVMs of the basal ganglia and 77 had AVMs of the thalamus. In this series, 113 (85%) of 133 patients had a prior hemorrhage. The median target volume was 2.7 cm(3) (range 0.1-20.7 cm(3)) and the median margin dose was 20 Gy (range 15-25 Gy).

RESULTS
Obliteration of the AVM eventually was documented on MR imaging in 78 patients and on angiography in 63 patients in a median follow-up period of 61 months (range 2-265 months). The actuarial rates documenting total obliteration after radiosurgery were 57%, 70%, 72%, and 72% at 3, 4, 5, and 10 years, respectively. Factors associated with a higher rate of AVM obliteration included
AVMs located in the basal ganglia, a smaller target volume, a smaller maximum diameter, and a higher margin dose. Fifteen (11%) of 133 patients suffered a hemorrhage during the latency period and 7 patients died. The rate of post-SRS AVM hemorrhage was 4.5%, 6.2%, 9.0%, 11.2%, and 15.4% at 1, 2, 3, 5, and 10 years, respectively. The overall annual hemorrhage rate was 4.7%. When 5 patients with 7 hemorrhages occurring earlier than 6 months after SRS were removed from this analysis, the annual hemorrhage rate decreased to 2.7%. Larger volume AVMs had a higher risk of hemorrhage after SRS. Permanent neurological deficits due to adverse radiation effects (AREs) developed in 6 patients (4.5%), and in 1 patient a delayed cyst developed 56 months after SRS. No patient died of AREs. Factors associated with a higher risk of symptomatic AREs were larger target volume, larger maximum diameter, lower margin dose, and a higher Pollock-Flickinger score.

CONCLUSIONS
Stereotactic radiosurgery is a gradually effective and relatively safe management option for deep-seated AVMs in the basal ganglia and thalamus. Although hemorrhage after obliteration did not occur in the present series, patients remain at risk during the latency interval between SRS and obliteration. The best candidates for SRS are patients with smaller volume AVMs located in the basal ganglia.

Stereotactic radiosurgery for arteriovenous malformations, Part 5: management of brainstem arteriovenous malformations.
Kano H, Kondziolka D, Flickinger JC, Yang HC, Flannery TJ, Niranjan A, Novotny J Jr, Lunsford LD.

Department of Neurological Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213, USA.

OBJECT
In this paper, the authors' goal was to define the long-term outcomes and risks of stereotactic radiosurgery (SRS) for arteriovenous malformations (AVMs) of the medulla, pons, and midbrain.

METHODS:
Between 1987 and 2006, the authors performed Gamma Knife surgery in 996 patients with brain AVMs; 67 patients had AVMs in the brainstem. In this series, 51 patients (76%) had a prior hemorrhage. The median target volume was 1.4 cm(3) (range 0.1-13.4 cm(3)). The median margin dose was 20 Gy (range 14-25.6 Gy).

RESULTS
Obliteration of the AVMs was eventually documented in 35 patients at a median follow-up of 73 months (range 6-269 months). The actuarial rates of documentation of total obliteration were 41%,
70%, 70%, and 76% at 3, 4, 5, and 10 years, respectively. Higher rates of AVM obliteration were associated only with a higher margin dose. Four patients (6%) suffered a hemorrhage during the latency period, and 2 patients died. The rate of AVM hemorrhage after SRS was 3.0%, 3.0%, and 5.8% at 1, 5, and 10 years, respectively. The overall annual hemorrhage rate was 1.9%. Permanent neurological deficits due to adverse radiation effects (AREs) developed in 7 patients (10%) after SRS, and a delayed cyst developed in 2 patients (3%). One patient died at an outside institution with symptoms of AREs and unrecognized hydrocephalus. Higher 12-Gy volumes and higher Spetzler-Martin grades were associated with a higher risk of symptomatic AREs. Ten of 22 patients who had ocular dysfunction before SRS had improvement, 9 were unchanged, and 3 were worse due to AREs. Eight of 14 patients who had hemiparesis before SRS improved, 5 were unchanged, and 1 was worse.

CONCLUSIONS
Although hemorrhage after obliteration did not occur in this series, patients remained at risk during the latency interval until obliteration occurred. Thirty-eight percent of the patients who had neurological deficits due to prior hemorrhage improved. Higher dose delivery in association with conformal and highly selective SRS is required for safe and effective radiosurgery.

Stereotactic radiosurgery for arteriovenous malformations, Part 6: multistaged volumetric management of large arteriovenous malformations.
Kano H, Kondziolka D, Flickinger JC, Park KJ, Parry PV, Yang HC, Sirin S, Niranjan A, Novotny J Jr, Lunsford LD.
Department of Neurological Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213, USA.

OBJECT
The object of this study was to define the long-term outcomes and risks of arteriovenous malformation (AVM) management using 2 or more stages of stereotactic radiosurgery (SRS) for symptomatic large-volume lesions unsuitable for surgery.

METHODS
In 1992, the authors prospectively began to stage the treatment of anatomical components to deliver higher single doses to AVMs with a volume of more than 10 cm(3). Forty-seven patients with such AVMs underwent volume-staged SRS. In this series, 18 patients (38%) had a prior hemorrhage and 21 patients (45%) underwent prior embolization. The median interval between the first-stage SRS and the second-stage SRS was 4.9 months (range 2.8-13.8 months). The median target
volume was 11.5 cm(3) (range 4.0-26 cm(3)) in the first-stage SRS and 9.5 cm(3) in the second-stage SRS. The median margin dose was 16 Gy (range 13-18 Gy) for both stages.

RESULTS
In 17 patients, AVM obliteration was confirmed after 2-4 SRS procedures at a median follow-up of 87 months (range 0.4-209 months). Five patients had near-total obliteration (volume reduction > 75% but residual AVM). The actuarial rates of total obliteration after 2-stage SRS were 7%, 20%, 28%, and 36% at 3, 4, 5, and 10 years, respectively. The 5-year total obliteration rate after the initial staged volumetric SRS with a margin dose of 17 Gy or more was 62% (p = 0.001). Sixteen patients underwent additional SRS at a median interval of 61 months (range 33-113 months) after the initial 2-stage SRS. The overall rates of total obliteration after staged and repeat SRS were 18%, 45%, and 56% at 5, 7, and 10 years, respectively. Ten patients sustained hemorrhage after staged SRS, and 5 of these patients died. Three of 16 patients who underwent repeat SRS sustained hemorrhage after the procedure and died. Based on Kaplan-Meier analysis (excluding the second hemorrhage in the patient who had 2 hemorrhages), the cumulative rates of AVM hemorrhage after SRS were 4.3%, 8.6%, 13.5%, and 36.0% at 1, 2, 5, and 10 years, respectively. This corresponded to annual hemorrhage risks of 4.3%, 2.3%, and 5.6% for Years 0-1, 1-5, and 5-10 after SRS. Multiple hemorrhages before SRS correlated with a significantly higher risk of hemorrhage after SRS. Symptomatic adverse radiation effects were detected in 13% of patients, but no patient died as a result of an adverse radiation effect. Delayed cyst formation did not occur in any patient after SRS.

CONCLUSIONS
Prospective volume-staged SRS for large AVMs unsuitable for surgery has potential benefit but often requires more than 2 procedures to complete the obliteration process. To have a reasonable chance of benefit, the minimum margin dose should be 17 Gy or greater, depending on the AVM location. In the future, prospective volume-staged SRS followed by embolization (to reduce flow, obliterate fistulas, and occlude associated aneurysms) may improve obliteration results and further reduce the risk of hemorrhage after SRS.

Kano H, Kondziolka D, Flickinger JC, Yang HC, Flannery TJ, Awan NR, Niranjan A, Novotny J Jr, Lunsford LD.

Department of Neurological Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213, USA.
OBJECT
The object of this study was to evaluate the outcomes and risks of repeat stereotactic radiosurgery (SRS) for incompletely obliterated cerebral arteriovenous malformations (AVMs).
METHODS
Between 1987 and 2006, Gamma Knife surgery was performed in 996 patients with AVMs. During this period, repeat SRS was performed in 105 patients who had incompletely obliterated AVMs at a median of 40.9 months after initial SRS (range 27.5-139 months). The median AVM target volume was 6.4 cm(3) (range 0.2-26.3 cm(3)) at initial SRS but was reduced to 2.3 cm(3) (range 0.1-18.2 cm(3)) at the time of the second procedure. The median margin dose at both initial SRS and repeat SRS was 18 Gy.

RESULTS
The actuarial rate of total obliteration by angiography or MR imaging after repeat SRS was 35%, 68%, 77%, and 80% at 3, 4, 5, and 10 years, respectively. The median time to complete angiographic or MR imaging obliteration after repeat SRS was 39 months. Factors associated with a higher rate of AVM obliteration were smaller residual AVM target volume (p = 0.038) and a volume reduction of 50% or more after the initial procedure (p = 0.014). Seven patients (7%) had a hemorrhage in the interval between initial SRS and repeat SRS. Seventeen patients (16%) had hemorrhage after repeat SRS and 6 patients died. The cumulative actuarial rates of new AVM hemorrhage after repeat SRS were 1.9%, 8.1%, 10.1%, 10.1%, and 22.4% at 1, 2, 3, 5, and 10 years, respectively, which translate to annual hemorrhage rates of 4.05% and 1.79% of patients developing new post-repeat-SRS hemorrhages per year for Years 0-2 and 2-10 following repeat SRS. Factors associated with a higher risk of hemorrhage after repeat SRS were a greater number of prior hemorrhages (p = 0.008), larger AVM target volume at initial SRS (p = 0.010), larger target volume at repeat SRS (p = 0.002), initial AVM volume reduction less than 50% (p = 0.019), and a higher Pollock-Flickinger score (p = 0.010). Symptomatic adverse radiation effects developed in 5 patients (4.8%) after initial SRS and in 10 patients (9.5%) after repeat SRS. Prior embolization (p = 0.022) and a higher Spetzler-Martin grade (p = 0.004) were significantly associated with higher rates of adverse radiation effects after repeat SRS. Delayed cyst formation occurred in 5 patients (4.8%) at a median of 108 months after repeat SRS (range 47-184 months).

CONCLUSIONS
Repeat SRS for incompletely obliterated AVMs increases the eventual obliteration rate. Hemorrhage after obliteration did not occur in this series. The best results for patients with incompletely obliterated AVMs were seen in patients with a smaller residual nidus volume and no prior hemorrhages.
Gamma Knife surgery for arteriovenous malformations in children.
Yen CP, Monteith SJ, Nguyen JH, Rainey J, Schlesinger DJ, Sheehan JP.
Department of Neurological Surgery, University of Virginia Health System, Charlottesville, Virginia 22908, USA.

OBJECT
The aim of this study was to evaluate the long-term imaging and clinical outcomes of intracranial arteriovenous malformations (AVMs) in children treated with Gamma Knife surgery (GKS).

METHODS
Between 1989 and 2007, 200 patients with AVMs who were 18 years of age or younger were treated at the University of Virginia Health System. Excluding 14 patients who had not reached 2-year follow-up, 186 patients comprised this study. Hemorrhage was the most common presenting symptom leading to the diagnosis of AVMs (71.5%). The mean nidus volume was 3.2 cm(3) at the time of GKS, and a mean prescription dose of 21.9 Gy was used.

RESULTS
After initial GKS, 49.5% of patients achieved total angiographic obliteration. Forty-one patients whose AVM nidi remained patent underwent additional GKS. The obliteration rate increased to 58.6% after a second or multiple GKS. Subtotal obliteration was achieved in 9 patients (4.8%). Forty-nine patients (26.3%) still had a patent residual nidus. In 19 patients (10.2%), obliteration was confirmed on MR imaging only. Ten patients had 17 hemorrhages during the follow-up period. The hemorrhage rate was 5.4% within 2 years after GKS and 0.8% between 2 and 5 years. Six patients developed neurological deficits along with the radiation-induced changes. Two patients developed asymptomatic meningiomas 10 and 12 years after GKS. After a mean clinical follow-up of 98 months, less than 4% of patients had difficulty attending school or developing a career.

CONCLUSIONS
Gamma Knife surgery offers a reasonable chance of obliteration of an AVM in pediatric patients. The incidence of symptomatic radiation-induced changes is relatively low; however, long-term clinical and imaging follow-up is required to identify delayed cyst formation and secondary tumors.
A modified radiosurgery-based arteriovenous malformation grading scale and its correlation with outcomes.


Department of Radiation Oncology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, USA.

PURPOSE
The Pittsburgh radiosurgery-based arteriovenous malformation (AVM) grading scale was developed to predict patient outcomes after radiosurgery and was later modified with location as a two-tiered variable (deep vs. other). The purpose of this study was to test the modified radiosurgery-based AVM score in a separate set of AVM patients managed with radiosurgery.

METHODS AND MATERIALS
The AVM score is calculated as follows: AVM score = (0.1)(volume, cc) + (0.02)(age, years) + (0.5)(location; frontal/temporal/parietal/occipital/intraventricular/corpus callosum/cerebellar = 0, basal ganglia/thalamus/brainstem = 1). Testing of the modified system was performed on 293 patients having AVM radiosurgery from 1992 to 2004 at the University of Pittsburgh with dose planning based on a combination of stereotactic angiography and MRI. The median patient age was 38 years, the median AVM volume was 3.3 cc, and 57 patients (19%) had deep AVMs. The median modified AVM score was 1.25. The median patient follow-up was 39 months.

RESULTS
The modified AVM scale correlated with the percentage of patients with AVM obliteration without new deficits (≤1.00, 62%; 1.01-1.50, 51%; 1.51-2.00, 53%; and >2.00, 32%; F = 11.002, R(2) = 0.8117, p = 0.001). Linear regression also showed a statistically significant correlation between outcome and dose prescribed to the margin (F = 25.815, p <0.001).

CONCLUSIONS
The modified radiosurgery-based AVM grading scale using location as a two-tiered variable correlated with outcomes when tested on a cohort of patients who underwent both angiography and MRI for dose planning. This system can be used to guide choices among observation, endovascular, surgical, and radiosurgical management strategies for individual AVM patients.
Neurosurgery. 2010 Jul;67(1):55-64; discussion 64.
Repeat Gamma Knife surgery for incompletely obliterated cerebral arteriovenous malformations.
Yen CP, Jain S, Haq IU, Jagannathan J, Schlesinger D, Sheehan J, Steiner L.

Lars Leksell Center for Gamma Surgery, Department of Neurological Surgery, University of Virginia Health Sciences System, Charlottesville, Virginia 22908, USA.

OBJECTIVE
The causes of failure after an initial Gamma procedure were studied, along with imaging and clinical outcomes, in a series of 140 patients with cerebral arteriovenous malformations (AVMs) treated with repeat Gamma Knife surgery (GKS).

METHODS
Causes of initial treatment failure included inaccurate nidus definition in 14 patients, failure to fill part of the nidus as a result of hemodynamic factors in 16, recanalization of embolized AVM compartments in 6, and suboptimal dose (<20 Gy) in 23. Nineteen patients had repeat GKS for subtotal obliteration of AVMs. In 62 patients, the AVM failed to obliterate despite correct target definition and adequate dose. At the time of retreatment, the nidus volume ranged from 0.1 to 6.9 cm³ (mean, 1.4 cm³), and the mean prescription dose was 20.3 Gy.

RESULTS
Repeat GKS yielded a total angiographic obliteration in 77 patients (55%) and subtotal obliteration in 9 (6.4%). In 38 patients (27.1%), the AVMs remained patent, and in 16 patients (11.4%), no flow voids were observed on magnetic resonance imaging. Clinically, 126 patients improved or remained stable, and 14 experienced deterioration (8 resulting from a rebleed, 2 caused by persistent arteriovenous shunting, and 4 related to radiation-induced changes).

CONCLUSION
By using repeat GKS, we achieved a 55% angiographic cure rate. Although radiation-induced changes as visualized on magnetic resonance imaging occurred in 48 patients (39%), only 4 patients (3.6%) developed permanent neurological deficits. These findings may be useful in deciding the management of AVMs in whom total obliteration after initial GKS was not achieved.

Gamma knife radiosurgery for arteriovenous malformations of basal ganglia, thalamus and brainstem--a retrospective study comparing the results with that for AVMs at other intracranial locations.


Department of Neuro Surgery, Neuro Sciences Centre, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India.

OBJECTIVE
The objective of this retrospective study was to study the outcome in patients with basal ganglia, thalamus and brainstem (central/deep) arteriovenous malformations (AVMs) treated with gamma knife radiosurgery (GKS) and to compare the results with that for AVMs at other intracranial locations.

METHODS AND RESULTS
The results of 53 patients with central AVMs and 255 patients with AVMs at other locations treated with GKS at our center between April 1997 and March 2005 with minimum follow-up of 1 year were analyzed. CENTRAL AVMS: Forty of these 53 AVMs were Spetzler-Martin grade III, 11 were grade IV, and 2 were grade V. The mean AVM volume was 4.3 cm\(^3\) (range 0.1-36.6 cm\(^3\)). The mean marginal dose given was 23.3 Gy (range 16-25 Gy). The mean follow-up was 28 months (range 12-96 months). Check angiograms were advised at 2 years after GKS and yearly thereafter in the presence of residual AVM till 4 years. Presence of a residual AVM on an angiogram at 4 years after radiosurgery was considered as radiosurgical failure. Complete obliteration of the AVM was documented in 14 (74%) of the 19 patients with complete angiographic follow-up. Significantly lower obliteration rates (37% vs. 100%) were seen in larger AVMs (>3 cm\(^3\)) and AVMs of higher (IV and V) Spetzler-Martin grades (28% vs. 100%). The 3- and 4-year actuarial rates of nidus obliteration were 68% and 74%, respectively. Eight patients (15%) developed radiation edema with a statistically significantly higher incidence in patients with AVM volume >3 cm\(^3\) and in patients with Spetzler-Martin grade IV and V AVMs. Five patients (9.4%) had hemorrhage in the period of latency.

COMPARISON OF RESULTS WITH AVMS AT OTHER LOCATIONS: Patients with central AVMs presented at a younger age (mean age 22.7 years vs. 29 years), with a very high proportion (81% vs. 63%) presenting with hemorrhage. Significantly higher incidence of radiation edema (15% vs. 5%) and lower obliteration rates (74% vs. 93%) were seen in patients with central AVMs.

CONCLUSIONS
GKS is an effective modality of treatment for central AVMs, though relatively lower obliteration rates and higher complication rates are seen compared to AVMs at other locations.
OBJECT
The purpose of this study was to examine the efficacy and toxicity of treating arteriovenous malformations (AVMs) with the model 3C Gamma Knife at the University of Washington Medical Center.

METHODS
Ninety-five evaluable patients with 99 treatable AVMs were treated at the University of Washington Medical Center from April 2000 through June 2005. The median patient age at the time of treatment was 40 years (range 6-68 years). The male to female patient ratio was 0.98:1. The median AVM volume treated was 3.8 cm³ (range 0.12-32 cm³). Forty-four percent of the patients had hemorrhaged prior to treatment. The median peripheral Gamma Knife surgery dose was 20 Gy with a median of 12 isocenters treated. The median follow-up duration was 38 months (range 3-91 months). Eighty-one percent of the patients had no previous stereotactic radiosurgery (SRS), whereas the remaining 19% had previously been treated with linear accelerator-based SRS.

RESULTS
The Kaplan-Meier estimated 6-year AVM obliteration rate for the entire cohort was 71.4%. The Kaplan-Meier estimated 6-year obliteration rate was 72% for patients having no prior SRS and 54.5% for those undergoing repeat SRS. The median time to AVM obliteration was 47 months, with 90% of the obliterations occurring between 24 and 58 months. Eight patients (7.4%) experienced late toxicities. There were 2 fatal bleeds and 13 (13.8%) nonfatal bleeds after Gamma Knife surgery.

CONCLUSIONS
Gamma Knife surgery is an effective treatment for AVMs, resulting in an excellent obliteration rate with acceptable toxicity.
Prospective staged volume radiosurgery for large arteriovenous malformations: indications and outcomes in otherwise untreatable patients.
Sirin S, Kondziolka D, Niranjan A, Flickinger JC, Maitz AH, Lunsford LD.
Department of Neurological Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania 15213, USA.

OBJECTIVE
The obliteration response of an arteriovenous malformation (AVM) to radiosurgery is strongly dependent on dose and volume. For larger volumes, the dose must be reduced for safety, but this compromises obliteration. In 1992, we prospectively began to stage anatomic components in order to deliver higher single doses to symptomatic AVMs > 15 ml in volume.

METHODS
During a 17-year interval at the University of Pittsburgh, 1040 patients underwent radiosurgery for a brain AVM. Out of 135 patients who had multiple procedures, 37 patients underwent prospectively staged volume radiosurgery for symptomatic otherwise unmanageable larger malformations. Twenty-eight patients who were managed before 2002 were included in this study to achieve sufficient follow-up in assessing the outcomes. The median age was 37 years (range, 13-57 yr). Thirteen patients had previous hemorrhages and 13 patients had attempted embolization. Separate anatomic volumes were irradiated at 3 to 8 months (median, 5 mo) intervals. The median initial AVM volume was 24.9 ml (range, 10.2-57.7 ml). Twenty-six patients had two stages and two had three-stage radiosurgery. Seven patients had repeat radiosurgery after a median interval of 63 months. The median target volume was 12.3 ml. (range, 4.2-20.8 ml.) at Stage I and 11.5 ml. (range, 2.8-22 ml.) at Stage II. The median margin dose was 16 Gy at both stages. Median follow-up after the last stage of radiosurgery was 50 months (range, 3-159 mo).

RESULTS
Four patients (14%) sustained a hemorrhage after radiosurgery; two died and two patients recovered with mild permanent neurological deficits. Worsened neurological deficits developed in one patient. Seizure control was improved in three patients, was stable in eight patients and worsened in two. Magnetic resonance imaging showed T2 prolongation in four patients (14%). Out of 28 patients, 21 had follow-up more than 36 months. Out of 21 patients, seven underwent repeat radiosurgery and none of them had enough follow- up. Of 14 patients followed for more than 36 months, seven (50%) had total, four (29%) near total, and three (21%) had moderate AVM obliteration.

CONCLUSIONS
Prospective staged volume radiosurgery provided imaging defined volumetric reduction or closure in a series of large AVMs unsuitable for any other therapy. After 5 years, this early experience suggests that AVM related symptoms can be stabilized and anticipated bleed rates can be reduced.

Radiosurgery for arteriovenous malformations with gamma-knife: a multivariate analysis of factors influencing the complete obliteration rate.
Fukuoka S, Takanashi M, Seo Y, Suematsu K, Nakamura J.

Department of Neurosurgery, Nakamura Memorial Hospital, Sapporo, Japan.

Abstract
Seventy-two patients with arteriovenous malformations (AVMs) were treated with gamma-knife and subsequently analyzed to determine what factors influenced the obliteration of AVMs. The volume of nidi ranged from 0.3 to 21.7 ml (mean 3.9 ml) and the marginal dose ranged from 9 to 31.5 Gy (mean 21.4 Gy). The cumulative obliteration rates of all cases were 41% at 2 years, 67% at 3 years, and 89% at 4 years. Multivariate analysis demonstrated that only the two variables of flow rate (P = 0.020) and dose planning with axial MRI (P = 0.045) had correlation with the obliteration rate. Other variables such as size, marginal dose, and embolization had no statistical correlation with the obliteration rate. It may be very important to evaluate the AVM flow rate to predict the effect of gamma-knife radiosurgery on AVMs, even when the nidi volumes are small.

Pan DH, Kuo YH, Guo WY, Chung WY, Wu HM, Liu KD, Chang YC, Wang LW, Wong TT.

Department of Neurosurgery, Taipei Veterans General Hospital, Taipei, Taiwan.

OBJECT
Studies on the efficacy of arteriovenous malformation (AVM) radiosurgery have largely been conducted in the adult population. Clinically, the results may not always be applicable to pediatric patients. Moreover, studies involving the pediatric population have largely comprised small- (< 3 cm3) and medium-sized (3-10 cm3) AVMs. For large (> 10 cm3) AVMs in children, sparse radiosurgical results are available. The current study was conducted to further clarify the role of radiosurgery in the treatment of pediatric AVMs.

METHODS
A retrospective analysis was performed of data obtained in 105 pediatric patients (< 18 years of age) with cerebral AVMs treated by Gamma Knife surgery (GKS) between 1993 and 2006. For statistical comparison the authors studied data acquired in 458 adult patients with AVMs treated during the same
period. The patients underwent follow-up magnetic resonance imaging at 6-month intervals. Cerebral angiography was used to confirm the obliteration of the AVM.
RESULTS
In pediatric patients, the AVM obliteration rate at 48 months after a primary GKS was 65%. Repeated GKS in those in whom primary treatments failed further ablated some AVMs, for an overall obliteration rate of 81%. The efficacy of GKS correlated with the size of the AVM: 91% for small, 86% for medium, and 64% for large AVMs. The treatments were associated with an 8% morbidity rate and < 1% mortality rate. Posttreatment hemorrhage occurred in 4 (4%) of 105 patients. Obliteration rates at 48 months of small and extremely large (> 20 cm3) AVMs were similar in the pediatric and adult groups, whereas AVMs between 3 and 10 cm3 responded less efficaciously in children (p = 0.042). The AVMs with volumes ranging from 10 to 20 cm3 were also associated with a lower obliteration rate in children at 48 months, but statistical significance was not reached (p = 0.279).

CONCLUSIONS
Gamma Knife surgery is an effective and safe treatment alternative for pediatric AVMs. The medium (3-10-cm3) and large (10-20-cm3) AVMs tend to respond less efficaciously than those of comparable size in adults.

Combined management of intracranial arteriovenous malformations with embolization and gamma knife radiosurgery: comparative evaluation of the long-term results.
Izawa M, Chernov M, Hayashi M, Iseki H, Hori T, Takakura K.

Department of Neurosurgery, Neurological Institute, Tokyo Women's Medical University, Tokyo 162-8666, Japan.

BACKGROUND
Volume reduction of large AVMs attained with endovascular embolization can be potentially helpful for their subsequent radiosurgical management. The objective of the present retrospective analysis was comparative evaluation of the long-term outcome after GKR for intracranial AVM performed with and without initial embolization of the nidus.

METHODS
The long-term outcome in 15 patients with intracranial AVM treated with initial embolization and subsequent GKR was evaluated and compared with the series of 237 patients treated during the same period solely with GKR. All patients were followed at least 2 years after radiosurgery.

RESULTS
Mean reductions of the nidus volume and score of the radiosurgery-based grading system for AVMs after embolization constituted 6.9 +/- 2.4 mL and 0.7 +/- 0.2, respectively (P < .001). Complete obliteration of the nidus after GKR was marked in 10 cases (67%). It was attained in 9 (90%) of 10 AVMs with postembolization nidus volume less than 12 mL, and in 1 (20%) of 5 with postembolization nidus volume more than 12 mL (P < .05). Delayed cyst formation was met once (7%). Obliteration and long-term morbidity rates did not differ significantly in patients treated with and without preradiosurgical nidus embolization, whereas nidus volume was seemingly larger in the former cohort.

CONCLUSIONS
Combined management with embolization and GKR may be effective for selected cases of large intracranial AVM. Radiosurgery preceded by partial nidus embolization does not associate with increased rate of long-term complications.

Arteriovenous malformations after Leksell gamma knife radiosurgery: rate of obliteration and complications.

Source
Department of Stereotactic and Radiation Neurosurgery, Na Homolce Hospital, Prague, Czech Republic.
Roman.Liscak@homolka.cz

Abstract
OBJECTIVE
Although relevant information exists regarding the chance of obliterating arteriovenous malformations (AVMs) using radiosurgery, the overall chance of cure after gamma knife radiosurgery is usually only extrapolated from a portion of all monitored patients. This chance and the risks involved in radiosurgery, including repeat treatment when necessary in a defined population of treated patients, were analyzed in our study.

METHODS
Between October 1992 and June 2000, gamma knife radiosurgery was performed on 330 patients with AVMs. The volume of the AVM nidus ranged from 0.15 to 28.6 cm (median, 3.9 cm). When complete obliteration was not achieved within 3 years, repeat radiosurgery was performed on 76 patients. The volume of the nidus for the second treatment ranged from 0.09 to 16.8 cm (median 2.9 cm). The result was reviewed in 300 (91%) patients after the first round of treatment and in 68 (89.5%) after the second round of treatment.

RESULTS
AVM obliteration was achieved in 222 (74%) patients after the first round of radiosurgery and in 47 (69%) after the second. The overall chance of cure was 92% (269 patients). Final angiography verified complete obliteration by 12 to 96 months (median, 25 mo) after initial radiosurgery. Smaller volume AVMs and the application of a higher radiation dose resulted in a higher chance of obliteration. The risk of rebleeding after radiosurgery was 2.1% annually until full obliteration, and the overall mortality from rebleeding was 1%. The risk of permanent morbidity after the first and second radiosurgery treatments were 2.7 and 2.9%, respectively. The cumulative risk of morbidity in both groups of patients was 3.4%.

CONCLUSION
Although one-quarter of the patients required that the treatment be repeated, gamma knife radiosurgery can offer a high cure rate for patients treated for AVMs with a low risk of morbidity and mortality from rebleeding during the latent period.

Seizure control of Gamma Knife radiosurgery for non-hemorrhagic arteriovenous malformations.
Lim YJ, Lee CY, Koh JS, Kim TS, Kim GK, Rhee BA.

OBJECTIVES
Although radiosurgery has been found to be a safe and effective alternative treatment, seizure outcome of arteriovenous malformation (AVM) radiosurgery has not been documented in detail. We report the effect of Gamma Knife radiosurgery (GKRS) on seizures associated with AVMs and discuss the various factors that influence the prognosis.

MATERIAL AND METHODS
Between 1992 and 2004, 246 patients were treated with GKRS for AVMs at Kyung-Hee medical center. Forty five (17.0%) patients have non-hemorrhagic AVMs and presenting symptom was seizure. Two patients of all were excluded from this study due to loss of follow-up after radiosurgery. In this study, retrospective analysis of clinical characteristics, radiologic findings, radiosurgical seizure outcome were performed.

RESULTS
There were 32 male and 11 female with age ranging from 10 to 74 years (mean 35 years). Type of seizure included: general tonic clonic (n = 28); focal motor or sensory (n = 7); partial complex (n = 8). The location of AVM was temporal (n = 18); frontal (n = 9); deep seated (n = 7): parietal (n = 5); occipital (n = 4). Follow-up period was from 8 months to 12 years (mean 46 months). Mean volume was 6.2 cc (2.7-20), mean marginal and maximal dosage was 19.5 (17-26) and 36.6 Gy (13-50).
During follow-up after radiosurgical treatment, 23 (53.5%) of 43 patients were seizure-free, 10 (23.3%) had significant improvement, were unchanged in 8 (18.6%) and aggravated in 2 (4.6%) patients. In 33 patients, follow-up angiography or MRI was performed. Complete obliteration was achieved in 16 (49.0%) patients, partial obliteration in 13 (39.0%). Four were unchanged (12.0%). Of 33 patients with follow-up performed, 26 were followed for over 2 years. Eleven (84.6%) of 13 patients with complete obliteration were seizure-free (p < 0.005). Four (36.3%) of 13 with partial obliteration and unchanged remained seizure-free. Fifteen patients had experienced intractable seizure before radiosurgery. After radiosurgery, seizures disappeared in 8 (53%) patients. Seizure frequently decreased in 5 (33%) and 2 patients (14%) were unchanged but none was aggravated. Five (71%) of 7 patients with complete obliteration were seizure-free and 2 (40%) of 5 patients with partial obliteration were seizure-free.

CONCLUSION
Up to now, controversy about resective surgery or radiosurgery as treatment of seizure related to AVMs still remains. In this study, we experienced that Gamma Knife radiosurgery is commonly performed to treat AVMs and can improve symptomatic seizure associated with AVMs. To clarify the mechanism of seizure control in AVMs radiosurgery is difficult, but it seems to be closely related to hemodynamic effects after radiosurgery.

Inoue HK.

Source
Restorative Neurosurgery, Institute of Neural Organization, Fujioka, Japan. chair.ino@instno-med.org

Abstract
OBJECT
Several adverse effects such as brain edema, necrosis, arterial stenosis, hemorrhage after obliteration, and delayed cyst formation have been reported as early and late complications of Gamma Knife surgery (GKS) for arteriovenous malformations (AVMs). These adverse effects seem to be decreased in a lower-dose treatment regimen compared with the classic higher margin doses of 25 Gy because the radiation insult to the surrounding tissue is minimized. Long-term results of lower-dose GKS for AVMs are presented.

METHODS
One hundred fourteen patients with AVMs were treated with lower-dose GKS (< or = 20-Gy margin dose). There were 68 male and 46 female patients, aged 10 to 68 years (mean 35.4 years).
The evaluation of AVM nidi and dose planning were performed using both angiography and MR imaging in all cases to exclude the surrounding brain tissue. The mean margin dose was 19.5 Gy. Total angiographically documented obliteration was achieved in 65 (85.5%) of 76 patients. Eleven patients underwent a second treatment, including staged treatment for large AVMs; total AVM obliteration has been achieved in six of them to date. Of 38 patients in whom no follow-up examination could be performed, 19 of them were healthy and 10 were lost from follow up. Nine patients experienced bleeding during the latency period, and four of them suffered lethal hemorrhage. Symptomatic early complications were extensive brain edema after repeated GKS in one patient and an adverse effect on the internal capsule in one. Delayed cyst formation was found in one patient as a late complication 10 years after treatment. No treatment-related death has been noted to date.

CONCLUSIONS
Lower-dose GKS is an effective and safe treatment for patients with AVMs and may decrease long-term adverse effects to the surrounding brain.

Long-term complications after gamma knife surgery for arteriovenous malformations.

Department of Neurosurgery, Neurological Institute, Tokyo Women's Medical University, Tokyo, Japan.
mizawa@nij.twmu.ac.jp

OBJECT
The authors analyzed of the long-term complications that occur 2 or more years after gamma knife surgery (GKS) for intracranial arteriovenous malformations (AVMs).

METHODS
Patients with previously untreated intracranial AVMs that were managed by GKS and followed for at least 2 years after treatment were selected for analysis (237 cases). Complete AVM obliteration was attained in 130 cases (54.9%), and incomplete obliteration in 107 cases (45.1%). Long-term complications were observed in 22 patients (9.3%). These complications included hemorrhage (eight cases), delayed cyst formation (eight cases), increase of seizure frequency (four cases), and middle cerebral artery stenosis and increased white matter signal intensity on T2-weighted magnetic resonance imaging (one case of each). The long-term complications were associated with larger nidi volume (p < 0.001) and a lobar location of the AVM (p < 0.01). Delayed hemorrhage was associated only with incomplete obliteration of the nidius (p < 0.05). Partial obliteration conveyed no benefit. Delayed cyst formation was associated with a higher maximal GKS dose (p < 0.001), larger
nidus volume ($p < 0.001$), complete nidus obliteration ($p < 0.01$), and a lobar location of the AVM ($p < 0.05$).

**CONCLUSIONS**

Incomplete obliteration of the nidus is the most important factor associated with delayed hemorrhagic complications. Partial obliteration does not seem to reduce the risk of hemorrhage. Complete obliteration can be complicated by delayed cyst formation, especially if high maximal treatment doses have been administered.


Analysis of nidus obliteration rates after gamma knife surgery for arteriovenous malformations based on long-term follow-up data: the University of Tokyo experience.

Department of Neurosurgery, The University of Tokyo Hospital, Tokyo, Japan. shinmasa@ka2.so-net.ne.jp

**OBJECT**

A large number of clinical studies have been made on treatment outcomes of radiosurgery for arteriovenous malformations (AVMs), but the reported obliteration rates following this treatment vary significantly, perhaps reflecting the different methods and timings of the imaging studies used.

**METHODS**

The authors retrospectively analyzed their experience with **gamma knife surgery in 400 patients with AVMs** (follow-up period 1-135 months, median 65 months), with special reference to the imaging modality used in each case. The calculated obliteration rates varied from 68.2 to 92%, depending on imaging modality and timing of evaluation. When only unquestionable imaging data such as demonstrations of a residual nidus on computerized tomography (CT) or magnetic resonance (MR) images or findings on angiograms were used in the calculation, **the obliteration rates were 72% at 3 years and 87.3% at 5 years**. Factors leading to a better obliteration rate were previous hemorrhage ($p = 0.0084$), smaller nidus ($p = 0.0023$), and higher radiation dose to the lesion's margin ($p = 0.0495$), as determined in a multivariate analysis. Factors leading to an earlier obliteration of the nidus were male sex ($p = 0.0001$), previous hemorrhage ($p = 0.0039$), smaller nidus diameter ($p = 0.0006$), and dose planning using angiography alone ($p = 0.0201$).

**CONCLUSIONS**

After the introduction of CT and MR images into dose planning, the conformity and selectivity of dosimetry improved remarkably, although the latency intervals until obliteration were prolonged. Imaging outcomes for AVMs should be evaluated using data provided by longer follow-up periods. The
timing of additional treatments for residual AVMs should be decided cautiously, considering the size of the AVM, the patient age and sex, and the history of hemorrhage before radiosurgery.
Radiosurgery for arteriovenous malformations of the basal ganglia, thalamus, and brainstem. Pollock BE, Gorman DA, Brown PD.

OBJECT

Although stereotactic radiosurgery is frequently performed for arteriovenous malformations (AVMs) in deep locations, outcomes after radiosurgery for these patients have not been well studied. The goal of this paper was to study these outcomes.

METHODS

Between 1990 and 2000, **56 patients underwent radiosurgery for AVMs located in the basal ganglia (10 patients), thalamus (30 patients), or brainstem (16 patients)**. The median age of these patients was 34.2 years. Thirty-five patients (62%) had experienced previous bleeding. The AVMs were classified Grade IIIB in 62% of patients and Grade IV in 38% according to the modified Spetzler-Martin Scale; the median radiosurgery-based AVM score was 1.83. The **median volume of the lesion was 3.8 cm³** and the median radiation dose delivered to its margin was 18 Gy. The median duration of follow-up review after radiosurgery was 45 months (range 3-121 months). In seven patients (12%) hemorrhage occurred at a median of 12 months after radiosurgery; five patients (9%) died and two recovered without any deficit. Permanent radiation-related complications occurred in six (12%) of 51 patients (excluding the five patients who died of hemorrhage) after one procedure and in three (18%) of 17 patients after repeated radiosurgery. **Obliteration of the AVM was noted in 24 patients (43%); obliteration was confirmed by angiography in 18 patients and by magnetic resonance [MR] imaging in six patients** after a single procedure and in 32 patients (57%; confirmed by angiography in 25 patients and by MR imaging in seven patients) after one or more procedures. Excellent outcomes (obliteration of the lesion without any new deficit) were obtained in 39% of patients after one radiosurgical procedure and in 48% after one or more procedures. Twelve (67%) of 18 patients with AVM scores lower than 1.5 had excellent outcomes compared with 15 (39%) of 38 patients with AVM scores greater than 1.5 (p = 0.053).

CONCLUSIONS

Less than half of the patients with deeply located AVMs were cured of the future risk of hemorrhage without new neurological deficits. This experience emphasizes the difficulty in treating patients with deeply located AVMs; the majority of whom are also poor candidates for resection or embolization.
OBJECT
Management options for arteriovenous malformations (AVMs) of the brainstem are limited. The long-term results of stereotactic radiosurgery for these disease entities are poorly understood. In this report the authors reviewed both neurological and radiological outcomes following stereotactic radiosurgery for brainstem AVMs over 15 years of experience.

METHODS
Fifty patients with brainstem AVMs underwent gamma knife surgery between 1987 and 2002. There were 29 male and 21 female patients with an age range of 7 to 79 years (median 35 years). Anatomical locations of these AVMs included the midbrain (39 lesions), pons (20 lesions), and medulla oblongata (three lesions). The radiation dose applied to the margin of the AVM varied from 12 to 26 Gy (median 20 Gy). Forty-five patients were followed up from 5 to 176 months (mean 72 months). The angiographically confirmed actuarial obliteration rate was 66% at the final follow-up examination. Two patients experienced a hemorrhage before obliteration. The annual hemorrhage rate was 1.7% for the first 3 years after radiosurgery and 0% thereafter. Patients who had received irradiation at two or fewer isocenters had higher obliteration rates (80% compared with 44% for > two isocenters, p = 0.006), and this was related to a more spherical nidus shape. The rate of persistent neurological complications in patients treated using magnetic resonance imaging-based dose planning after 1993 was 7%, compared with 20% in patients treated before 1993. An older patient age, a lesion located in the tectum, and a higher radiosurgery-based score were significantly associated with greater neurological complications.

CONCLUSIONS
Stereotactic radiosurgery provided complete obliteration of AVMs in two thirds of the patients with a low risk of latency-interval hemorrhage. Better three-dimensional imaging studies and conformal dose planning reduced the risk of adverse radiation effects. Younger patients harboring more spherical AVMs that did not involve the tectal plate had the best outcomes.
Patient outcomes after arteriovenous malformation radiosurgical management: results based on a 5- to 14-year follow-up study.
Pollock BE, Gorman DA, Coffey RJ.

Department of Neurologic Surgery, Division of Radiation Oncology, Mayo Clinic and Foundation, 200 First Street SW, Rochester, MN 55905, USA. pollock.bruce@mayo.edu

OBJECTIVE
Radiosurgery is commonly performed for patients with small to medium-sized arteriovenous malformations (AVMs). However, few articles present overall outcomes after one or more radiosurgical procedures, and few data are available for periods longer than 5 years after AVM radiosurgery.

METHODS
Between 1990 and 1997, 144 patients underwent AVM radiosurgery and had angiographic follow-up. Of these patients, 112 (78%) had Spetzler-Martin Grade III or greater AVMs; 37 (26%) were located in the basal ganglia, thalamus, or brainstem. Twenty-six patients (18%) underwent repeat radiosurgery. The mean follow-up of 15 patients who died as a result of AVM bleeding or underwent AVM resection after the initial radiosurgery was 22 months (range, 3-47 mo); the mean follow-up of the remaining 129 patients was 86 months (range, 23-169 mo).

RESULTS
Excellent (obliteration without deficit, n = 96) or good (obliteration with minor deficit, n = 9) outcomes were achieved in 73% of patients after one or more radiosurgical procedures. Twenty patients (14%) sustained major deficits (n = 15; five had obliteration) or died (n = 5) after radiosurgery. Sixteen patients (11%) had unchanged neurological examinations but persistent arteriovenous shunting. Five patients (4%) required surgery (cystoperitoneal shunting, n = 1; AVM resection, n = 4) at a median of 65 months after radiosurgery because of symptomatic cyst formation or persistent edema. The radiosurgery AVM score correlated with both excellent (R(2) = -0.93, P = 0.003) and excellent or good (R(2) = -0.92, P = 0.004) outcomes.

CONCLUSION
The majority of AVM patients are protected from the risk of future hemorrhage and continue their normal daily activities after radiosurgery. Late complications requiring treatment are rare but can occur many years after patients are considered cured of their AVMs. Overall outcomes after AVM radiosurgery seem to be predicted accurately by the described method.
Management of patients with brain arteriovenous malformations.
Söderman M, Andersson T, Karlsson B, Wallace MC, Edner G.

Source
Department of Neuroradiology, Karolinska Hospital, S-17176, Stockholm, Sweden.

Abstract
Arteriovenous malformations (AVMs) of the brain, which are probably genetically determined, are errors in the development of the vasculature that, together with the effects of blood flow, may lead to a focal arteriovenous shunt. Clinically, the adult patient may present with acute or chronic neurological symptoms—fixed or unstable—such as deficits, seizures or headache. Sometimes the lesion is an incidental finding. In about half of the patients, the revealing event is an intracranial haemorrhage. The prevalence of AVM in the western world is probably <0.01% and the detection rate is about one per 100,000 person-years. Most AVMs are revealed in patients 20-40 years of age. Therefore, the risk of developing neurological symptoms from an AVM, usually because of haemorrhage, increases with patient age. In the young adult population, AVMs are significant risk factors for hemorrhagic stroke. This risk increases with AVM volume and is higher in centrally located AVMs. Almost all patients with AVM are subjected to treatment, either by surgery, radiosurgery or embolisation, with the functional aim of reducing the risk of haemorrhage or to alleviate neurological symptoms with an acceptable treatment risk. Few neurocentres have physicians highly skilled in all treatment modalities. Therefore, the prescribed treatment may not be defined from an objective assessment of what is optimal for each individual patient, but rather from local expertise. In this context, more and better data about the natural history and the outcome of different treatments, as well as predictive models, would be valuable to help to optimise the management. Management strategies obviously differ according to local preferences, but results presented in the literature suggest the following strategy: (I) cortically located AVMs with a nidus volume <10 ml could be operated, with or without presurgical embolisation, unless there is a single feeder that can easily be catheterised and embolised for obliteration or other obvious target for embolisation, such as pseudoaneurysms or large fistulae; (II) centrally located AVMs with a nidus volume <10 ml should be treated by radiosurgery, unless suitable for embolisation as indicated above; (III) patients harbouring AVMs with a nidus volume >10 ml could benefit from targeted partial embolisation followed by radiosurgery or surgery, depending on the angioarchitecture; and (IV) AVMs >20 ml nidus volume usually have a high treatment risk with any treatment modality and are not obvious targets for treatment at all.
Hemorrhage risks and obliteration rates of arteriovenous malformations after gamma knife radiosurgery.
Inoue HK, Ohye C.

Source
Restorative Neurosurgery, Institute of Neural Organization and Gamma Knife Center, Hidaka Hospital, Fujioka, Japan. hkinoue@instnf.or.jp

Abstract

OBJECT
The purpose of this study was to analyze the risk of hemorrhage and the obliteration rate after treatment of patients with arteriovenous malformations (AVMs).

METHODS
Between 1991 and 1995, 115 patients were treated using gamma knife radiosurgery (GKS). Surgical planning was based on angiograms and three-dimensional images. The angiographic features of the AVMs and the risk factors for hemorrhage were then evaluated. Hemorrhages occurred in eight patients (7%) 7 to 42 months after GKS. Based on AVM morphology, the rates of hemorrhage were five (7.6%) of 66 for AVMs with a single draining vein, seven (14%) of 66 for AVMs with deep drainage, four (26.7%) of 15 for AVMs with a varix, four (28.6%) of 14 for AVMs with venous obstruction, eight (17.0%) of 47 for high-flow (shunt- and mixed-type) AVMs, and five (35.7%) of 14 for large AVMs with a volume of more than 10 cm3. No hemorrhages were observed in association with low-flow (moyamoya-type) AVMs in this series. Total AVM obliteration was achieved in 81.3% of 80 patients who underwent angiography. The obliteration rate was 91.3% for moyamoya-type AVMs and 67.6% for shunt- and mixed-type AVMs. Early obliteration within 12 months was achieved in 63% of the moyamoya-type AVMs.

CONCLUSIONS
Moyamoya-type AVMs seem to be at risk for post-GKS hemorrhage. Intravascular embolization should be considered prior to GKS for mixed- and shunt-type AVMs in an attempt to reduce the hemodynamic stress and thereby decrease the risk of hemorrhage.
**J Neurosurg. 2002 Dec;97(5 Suppl):471-3.**
Impact on the quality of life of patients with arteriovenous malformations during the latent interval between gamma knife radiosurgery and lesion obliteration.
Lai EH, Lun SL.

Department of Neurosurgery, Queen Elizabeth Hospital, Hong Kong, People's Republic of China.

**OBJECT**
The aim of this study was to measure the quality of life (QOL) in patients with cerebral arteriovenous malformations (AVMs) receiving gamma knife treatment before total AVM obliteration. Quality of life was assessed as it related to the knowledge of rebleeding risk during the waiting period, AVM symptoms, and previous bleeding.

**METHODS**
Thirty-nine patients age 18 years or older without other medical problems were asked to complete a questionnaire that included demographic variables, immediate effect of gamma knife radiosurgery, symptoms of AVM, previous hemorrhage, and the Duke-University of North Carolina Health Profile (63 items).

**CONCLUSIONS**
The QOL of patients with cerebral AVM during the waiting period after undergoing gamma knife treatment was affected by irreversible physical disabilities rather than the knowledge of hemorrhage risk and bleeding experience.

---

Gamma knife outcome models as a reference standard in the embolisation of cerebral arteriovenous malformations.
Söderman M, Rodesch G, Karlsson B, Lax I, Lasjaunias P.

**Source**
Department of Neuroradiology, Karolinska Hospital, Sweden.

**Abstract**
**BACKGROUND**
We sought to utilise outcome models from Gamma Knife radiosurgery (GKRS) to cerebral arteriovenous malformations (AVM) as a reference standard in assessing the clinical outcome of embolisation, thus comparing the outcomes of two different management alternatives, in the same patients.
METHODS
87 consecutive patients with 88 AVM were admitted during 1997-1999 for initial embolisation of an AVM. The clinical outcomes were recorded prospectively. Angiography under stereotactic conditions with measurement of AVM volume was performed before and after embolisation. GKRS outcome models were used to predict obliteration rate, complication rate and risk of haemorrhage before and after embolisation. The clinical outcome of embolisation followed by predicted outcome of adjunct GKRS was then compared with the predicted outcome of GKRS as the only treatment.

FINDINGS
Eight patients were subjected to microcatheterisation but not to embolisation. By the end of the study period, embolisation had been terminated in 55 patients out of 80 (69%). The predicted outcome of GKRS alone was 58 obliterations and 12 complications while that of the combined management was 58 obliterations and 15 complications. The difference was not significant on the p < 0.1 level.

INTERPRETATION
Volume measurement from angiography and outcome models from Gamma Knife radiosurgery are useful as a reference standard in the management of AVM. Absolute volume reduction from embolisation is most prominent for AVM > 10 ml and thus facilitates subsequent radiosurgery. For AVM < or = 10 ml, GKRS as the only treatment can be an alternative to primary embolisation, particularly if no significant volume reduction or obviously beneficial effect of targeted embolisation is expected. Further prospective studies are needed to identify subgroups in which one treatment has advantages over the other.

Medication is the standard treatment for the management of patients with movement disorders. However, there is a fraction of patients with insufficient effect or bothersome side-effects of pharmaceuticals. Deep brain stimulation (DBS) and surgical lesioning of the thalamus and basal ganglia are invasive neurosurgical procedures, with established success rates. In some patients these invasive options are contraindicated. In addition DBS is a very costly treatment alternative with high expenses for the implanted electrodes and with necessity for changing of the implanted batteries on a regular basis.

Stereotactic radiosurgery with the Gamma Knife (GK) has been used as a lesioning technique for patients seeking a non-invasive treatment alternative and for medication-intolerable patients, who are unable to undergo DBS or lesioning due to comorbid medical conditions:

GK thalamotomy is a non-invasive treatment alternative for patients with movement disorders providing relief from tremor equivalent in ca 80% of treated patients. Functional lesions may be made safely and accurately using gamma knife radiosurgical techniques. Long-term follow up indicates that relief of tremor is well maintained. The efficacy appears to be equivalent to that reported for open techniques that use radiofrequency lesioning methods with electrophysiological guidance. Complications after Gamma Knife thalamotomies are very infrequent. The use of functional Gamma Knife lesioning to treat movement disorders is particularly attractive in older patients and in those with major systemic diseases or coagulopathies; its use in the general movement disorder population seems reasonable as well.

Selected Literature 1996-2012: Gamma Knife Thalamotomy for Movement Disorders (and other functional indications)


Source
Abstract

BACKGROUND
No prospective study of gamma knife thalamotomy for intractable tremor has previously been reported.

OBJECTIVE
To clarify the safety and optimally effective conditions for performing unilateral gamma knife (GK) thalamotomy for tremors of Parkinson disease (PD) and essential tremor (ET), a systematic postirradiation 24-month follow-up study was conducted at 6 institutions. We present the results of this multicenter collaborative trial.

METHODS:
In total, 72 patients (PD characterized by tremor, n = 59; ET, n = 13) were registered at 6 Japanese institutions. Following our selective thalamotomy procedure, the lateral part of the ventralis intermedius nucleus, 45% of the thalamic length from the anterior tip, was selected as the GK isocenter. A single 130-Gy shot was applied using a 4-mm collimator. Evaluation included neurological examination, magnetic resonance imaging and/or computerized tomography, the unified Parkinson's disease rating scale (UPDRS), electromyography, medication change, and video observations.

RESULTS
Final clinical effects were favorable. Of 53 patients who completed 24 months of follow-up, 43 were evaluated as having excellent or good results (81.1%). UPDRS scores showed tremor improvement (parts II and III). Thalamic lesion size fluctuated but converged to either an almost spherical shape (65.6%), a sphere with streaking (23.4%), or an extended high-signal zone (10.9%). No permanent clinical complications were observed.

CONCLUSION
GK thalamotomy is an alternative treatment for intractable tremors of PD as well as for ET. Less invasive intervention may be beneficial to patients.

Gamma knife radiosurgery for movement disorders: a concise review of the literature.
Elaimy AL, Arthurs BJ, Lamoreaux WT, Demakas JJ, Mackay AR, Fairbanks RK, Greeley DR, Cooke BS, Lee CM.

Source
Gamma Knife of Spokane, 910 W 5th Ave, Suite 102, Spokane, WA 99204, USA.
Abstract
Medication is the predominant method for the management of patients with movement disorders. However, there is a fraction of patients who experience limited relief from pharmaceuticals or experience bothersome side-effects of the drugs. Deep brain stimulation (DBS) and surgical lesioning of the thalamus and basal ganglia are respected neurosurgical procedures, with valued success rates and a very low incidence of complications. Despite these positive outcomes, DBS and surgical lesioning procedures are contraindicated for some patients. Stereotactic radiosurgery with the Gamma Knife (GK) has been used as a lesioning technique for patients seeking a non-invasive treatment alternative and for medication-intolerable patients, who are unable to undergo DBS or lesioning due to comorbid medical conditions. Tremors of various etiologies are treated using GK thalamotomy, which targets the ventralis intermedius nucleus. GK thalamotomy produces favorable outcomes when treating tremors, with success rates ranging from 80-100%. In contrast, GK pallidotomy targets the internal globus pallidus, and is used in treating bradykinesia, rigidity, and dyskinesia. Although radiosurgery has proven beneficial for tremors, radiosurgical pallidotomy for bradykinesia, rigidity, and dyskinesia remains questionable, with mixed success rates in the literature that ranges from 0-87%. We suggest that GK thalamotomy be offered along with other neurosurgical approaches as a feasible treatment option to patients who prefer the non-invasive nature of radiosurgery and to those who are unqualified candidates for the neurosurgical alternatives. Also, we advise that patients with bradykinesia, rigidity, and dyskinesia be educated about the variability in the literature pertaining to GK pallidotomy before proceeding with treatment.

Young RF, Li F, Vermeulen S, Meier R.

Source
Northwest Hospital Gamma Knife Center, Seattle, Washington 98133, USA. rfy127@hotmail.com

Abstract
OBJECT
The goal of this report was to describe the safety and effectiveness of nucleus ventralis intermedius (VIM) thalamotomy performed with the Leksell Gamma Knife (GK) for the treatment of essential tremor (ET).

METHODS
One hundred seventy-two patients underwent a total of 214 VIM thalamotomy procedures with the Leksell GK between February 1994 and March 2007 for treatment of disabling ET. Eleven patients were lost to follow-up less than 1 year after the procedures, so that in this report the authors describe the
results in 161 patients who underwent a total of 203 thalamotomies (119 unilateral and 42 bilateral).
RESULTS
There were statistically significant decreases (p < 0.0001) in tremor scores for both writing and drawing. The mean postoperative follow-up duration for all patients was 44 +/- 33 months. Fifty-four patients have been followed for more than 60 months post treatment. There were 14 patients who suffered neurological side effects that were temporary (6) or permanent (8), which accounted for 6.9% of the 203 treatments. All complications were related to lesions that grew larger than expected.

CONCLUSIONS
A VIM thalamotomy with the Leksell GK offers a safe and effective alternative for surgical treatment of ET. It is particularly applicable to patients who are not ideal candidates for deep brain stimulation but can be offered to all patients who are considering surgical intervention for ET.

Treatment of functional disorders with gamma knife thalamotomy.
Ohye C, Shibazaki T.

Source
Hidaka Hospital, Functional and Gamma Knife Surgery Center, Takasaki, Gunma, Japan.
stereohye@dan.wind.ne.jp

Abstract
Gamma knife (GK) thalamotomy for functional disorders, primarily Parkinson disease and central pain, are described herein. The goal was to extend our present indications for selective thalamotomy. Our target for tremor surgery is about 45% of the thalamic length. Thus, this principle was applied to deciding the GK thalamotomy target. In most of our cases, the protocol was 130 Gy, delivered in one shot with a 4-mm collimator. The time courses of thalamic lesion changes and clinical improvement after irradiation were assessed. Thus, despite thalamic reaction changes being variable, we achieved a clinical success rate of approximately 80% with negligible complications.
OBJECTIVES
The purpose of this study was to evaluate the results following Gamma Knife thalamotomy (GKT) for medically refractory essential tremor in a series of patients in whom open surgical techniques were not desirable.

METHODS
Thirty-one patients underwent GKT for disabling essential tremor after medical therapy had failed. Their mean age was 77 years. Most patients were elderly or had concomitant medical illnesses. A single 4-mm isocenter was used to target a maximum dose of 130 or 140 Gy to the nucleus ventralis intermedius. Items from the Fahn-Tolosa-Marin clinical tremor rating scale were used to grade tremor and handwriting before and after radiosurgery.

RESULTS
The median follow-up was 36 months. In the group of 26 evaluable patients, the mean tremor score (+/- standard deviation) was 3.7 +/- 0.1 preoperatively and 1.7 +/- 0.3 after radiosurgery (p < 0.000015). The mean handwriting score was 2.8 +/- 0.2 before GKT and 1.7 +/- 0.2 afterward (p < 0.0002). After radiosurgery, 18 patients (69%) showed improvement in both action tremor and writing scores, 6 (23%) only in action tremor scores, and 3 (12%) in neither tremor nor writing. Permanent mild right hemiparesis and speech impairment developed in 1 patient 6 months after radiosurgery. Another patient had transient mild right hemiparesis and dysphagia.

CONCLUSIONS
Gamma Knife thalamotomy is a safe and effective therapy for medically refractory essential tremor. Its use is especially valuable for patients ineligible for radiofrequency thalamotomy or deep brain stimulation. Patients must be counseled on potential complications, including the low probability of a delayed neurological deficit.
Neurosurg Focus. 2007;23(6):E3.
Stereotactic radiosurgery for functional disorders.
Friehs GM, Park MC, Goldman MA, Zerris VA, Norén G, Sampath P.

Department of Clinical Neurosciences Program in Neurosurgery and New England Gamma Knife Center, Warren Alpert Medical School of Brown University, Rhode Island Hospital, Providence, Rhode Island, USA. gfriehs@yahoo.com

Abstract
Stereotactic radiosurgery (SRS) with the Gamma Knife and linear accelerator has revolutionized neurosurgery over the past 20 years. The most common indications for radiosurgery today are tumors and arteriovenous malformations of the brain. Functional indications such as treatment of movement disorders or intractable pain only contribute a small percentage of treated patients. Although SRS is the only noninvasive form of treatment for functional disorders, it also has some limitations: neurophysiological confirmation of the target structure is not possible, and one therefore must rely exclusively on anatomical targeting. Furthermore, lesion sizes may vary, and shielding adjacent radiosensitive neural structures may be difficult or impossible. The most common indication for functional SRS is the treatment of trigeminal neuralgia. Radiosurgical treatment for epilepsy and certain psychiatric illnesses is performed in several centers as part of strict research protocols, and radiosurgical pallidotomy or medial thalamotomy is no longer recommended due to the high risk of complications. Radiosurgical ventrolateral thalamotomy for the treatment of tremor in patients with Parkinson disease or multiple sclerosis, as well as in the treatment of essential tremor, may be indicated for a select group of patients with advanced age, significant medical conditions that preclude treatment with open surgery, or patients who must receive anticoagulation therapy. A promising new application of SRS is high-dose radiosurgery delivered to the pituitary stalk. This treatment has already been successfully performed in several centers around the world to treat severe pain in patients with end-stage cancer.

Gamma knife thalamotomy for multiple sclerosis tremor.
Mathieu D, Kondziolka D, Niranjan A, Flickinger J, Lunsford LD.

Department of Neurological Surgery, University of Pittsburgh, Center for Image-Guided Neurosurgery, Pittsburgh, PA 15213, USA.

BACKGROUND
Some patients with MS suffer from disabling tremor. Improvement with medical treatment is modest, at best. Stereotactic surgery targeting the vim nucleus of the thalamus has been successful in alleviating
MS tremor. Gamma knife radiosurgery represents a minimally invasive alternative to radiofrequency lesioning and DBS that can provide improvement in patients suffering from essential and parkinsonian tremor. We reviewed our experience with GK thalamotomy in the management of six consecutive patients suffering from disabling MS tremor.

**METHODS**
The median age at the time of radiosurgery was 46 years (range, 31 to 57 years). Intention tremor had been present for a median of three years (range 8 months to 12 years). One 4-mm isocenter was used to deliver a median maximum dose of 140 Gy (range, 130-150 Gy) to the vim nucleus of the thalamus opposite the side of the most disabling tremor. Clinical outcome was assessed using the Fahn-Tolosa-Marin scale.

**RESULTS**
The median follow-up was 27.5 months (range, 5-46 months). All patients experienced improvement in tremor after a median latency period of 2.5 months. More improvement was noted in tremor amplitude than in writing and drawing ability. In four patients, the tremor reduction led to functional improvement. One patient suffered from transient contralateral hemiparesis, which resolved after brief corticosteroid administration. No other complication was seen.

**CONCLUSION**
Gamma knife radiosurgical thalamotomy is effective as a minimally invasive alternative to stereotactic surgery for the palliative treatment of disabling MS tremor.

From selective thalamotomy with microrecording to gamma thalamotomy for movement disorders. Ohye C.

**Source**
Functional and Gamma Knife Surgery Center, Hidaka Hospital, Takasaki, Gunma, Japan.
stereohye@dan.wind.ne.jp

**Abstract**
A theoretical and practical process from microrecording-guided thalamotomy to gamma knife thalamotomy was briefly reviewed. Based on our own experiences of selective thalamotomy with microrecording, we are trying to apply gamma knife to the treatment of movement disorders. An important technical problem is how to determine the exact thalamic target. At first we refer to the posterior commissure and coordinate of the standard atlas for approximately determining the lateral part of the ventral intermediate nucleus. Then the point is further corrected by anatomical landmark (45% of the thalamic length) to compensate the individual difference. A final lesion is made by gamma knife using a 4-mm collimator, 130 Gy in 1 shot. The average delay of clinical improvement is
about 6 months after irradiation. Thus far the results are satisfactory, being 80-85% successful without any noticeable complications. Only 3 days of hospitalization with minimal invasion could be a big advantage for the patient. Further technical progress may improve the clinical results in the future.

Neurophysiological evaluation of the optimum target in gamma thalamotomy: indirect evidence.
Sato S, Ohye C, Shibazaki T, Zama A, Cai X.
Functional and Gamma Knife Surgery Center, Hidaka Hospital, Takasaki, Gunma, Japan.
sumito@ba.mbn.or.jp

Abstract
Gamma thalamotomy has been useful for the treatment of Parkinson's disease and other movement disorders, but it has disadvantages, such as a delayed clinical effect after irradiation and the inaccuracy of targeting because depth recording is not available. Therefore, we sought to determine the optimum target in gamma thalamotomy based on the results of conventional selective thalamotomy with reference to the AC-PC line. To obtain indirect support for the appropriateness of the optimum target, we performed depth recording around the region of the estimated optimum target based on the results of conventional thalamotomy. Four patients with tremor caused by Parkinson's disease or essential tremor were used as subjects after they gave their fully informed consent. The targets were determined as points 6-8 mm anterior to the posterior commissure, 4-6 mm dorsal to the level of the intercommissural line, and 15-17 mm lateral from the midline. Rhythmic discharge time-locked to tremor and/or kinesthetic neurons were found within the expected target area in all patients. Finally, in all cases, the tremor was abolished without complications after coagulative lesions were made with dual coagulation needles to cover the supposed Vim zone according to the depth recording. We considered that the target point determined in the same way as in gamma thalamotomy is suitable from an anatomophysiological perspective.

Gamma knife thalamotomy for movement disorders: evaluation of the thalamic lesion and clinical results.

Ohye C, Shibazaki T, Sato S.

Functional and Gamma Knife Surgery Center, Hidaka Hospital, Gunma, Japan.
stereohye@dan.wind.ne.jp

**OBJECT**

The authors studied the effects of gamma knife thalamotomy (GKT) on Parkinson disease-related tremor and essential tremor before and after reloading of radioactive cobalt.

**METHODS**

Based on experience in stereotactic thalamotomy aided by depth microrecording, the target was located at the lateral border of the thalamic ventralis intermedius nucleus (VIM). For more precise targeting, the percentage representation of the thalamic VIM in relation to the entire thalamic length is useful. The location of the target was determined on magnetic resonance (MR) imaging and computerized tomography scanning. A maximum dose of 130 Gy was delivered to the target by using a single isocenter with the 4-mm collimator. In more recent cases, a systematic follow-up examination was performed at 3, 6, 12, 18, and 24 months after GKT. Since 1993, the authors have treated 70 patients with PD. Throughout the series the same dosimetric technique has been used. The course after GKT was compared between the 25 cases with PD treated before reloading and the 35 cases treated after reloading. In the majority (80-85%) treated after reloading, tremor and rigidity were reduced around 6 months after GKT. In the cases treated before reloading this effect took approximately 1 year. The thalamic reaction on MR imaging showed the same two lesion types in both series: a restricted and a diffuse. After reloading the restricted lesion was more frequent and the lesion volume was smaller.

**CONCLUSIONS**

The shorter delay in clinical improvement and smaller lesion size may be related to an increased radiation dose.
OBJECT
The treatment of Parkinson disease and other kinds of involuntary movement by gamma knife radiosurgery (GKS) is presented. This is an extension of previous work. The clinical course and thalamic lesions were the main factors examined.

METHODS
Seventeen new cases were added to the previously reported 36 cases. The course and results for the whole series of 53 patients were examined. Treatment was undertaken using a single 4-mm collimator shot to deliver 130 Gy to the target. The target was determined in the previously treated patients by using classic methods involved in conventional stereotactic thalamotomy with microrecording. More recently, target localization has been performed by relating the target point to the total length of the thalamus. Points may then be defined as percentages of that length measured from the anterior pole. Targets can then be determined in relationship to the appropriate percentage. Thirty-five patients have been followed for more than 2 years and the longest follow up was 8 years. Two kinds of thalamic lesion were seen after GKS. Volumetric analysis on MR imaging revealed that the larger lesion was 400 to 500 mm3 at the beginning and gradually decreased in size. The smaller lesion occupied approximately 200 mm3 and also shrank over several months. Eighty percent of the treated cases showed good results and no significant complications, with the tremor subsiding at 1 year (Type 1). Several cases deviated from this standard course in four different ways (Types 2-5). If tremor persisted, conventional stereotactic thalamotomy with microrecording was performed. During such operations, normal neuronal activity was recorded from the region adjacent to the GKS thalamotomy target. This was the region showing a high signal on MR imaging. The activity patterns included the rhythmical grouped discharge of tremor rhythm.

CONCLUSIONS
Gamma thalamotomy for functional disorders is still under development, but because the results with careful target planning are satisfactory, there are grounds for increasing optimism.
Gamma knife thalamotomy for treatment of tremor: long-term results.

Young RF, Jacques S, Mark R, Kopyov O, Copcutt B, Posewitz A, Li F.

Neuroscience Institute and Gamma Knife Centers, Good Samaritan Hospital, Los Angeles, California, USA.

OBJECT
The purpose of this study was to investigate the long-term effects of gamma knife thalamotomy for treatment of disabling tremor.

METHODS
One hundred fifty-eight patients underwent magnetic resonance imaging-guided radiosurgical nucleus ventralis intermedius (VIM) thalamotomy for the treatment of parkinsonian tremor (102 patients), essential tremor (52 patients), or tremor due to stroke, encephalitis, or cerebral trauma (four patients). Preoperative and postoperative blinded assessments were performed by a team of independent examiners skilled in the evolution of movement disorders. A single isocenter exposure with the 4-mm collimator helmet of the Leksell gamma knife unit was used to make the lesions. In patients with Parkinson's disease 88.3% became fully or nearly tremor free, with a mean follow up of 52.5 months. Statistically significant improvements were seen in Unified Parkinson's Disease Rating Scale tremor scores and rigidity scores, and these improvements were maintained in 74 patients followed 4 years or longer. In patients with essential tremor, 92.1% were fully or nearly tremor free postoperatively, but only 88.2% remained tremor free by 4 years or more post-GKS. Statistically significant improvements were seen in the Clinical Rating Scale for tremor in essential tremor patients and these improvements were well maintained in the 17 patients, followed 4 years or longer. Only 50% of patients with tremor of other origins improved significantly. One patient sustained a transient complication and two patients sustained mild permanent side effects from the treatments.

CONCLUSIONS
Gamma knife VIM thalamotomy provides relief from tremor equivalent to that provided by radiofrequency thalamotomy or deep brain stimulation, but it is safer than either of these alternatives. Long-term follow up indicates that relief of tremor is well maintained. No long-term radiation-induced complications have been observed.
Functional outcomes after gamma knife thalamotomy for essential tremor and MS-related tremor.
Niranjan A, Kondziolka D, Baser S, Heyman R, Lunsford LD.

Department of Neurological Surgery, University of Pittsburgh, Pittsburgh, PA, USA.

Abstract
Twelve patients with a median age of 75 years underwent gamma knife thalamotomy for essential tremor (ET) (n = 9) or MS-related tremor (n = 3). All 11 evaluable patients noted improvement in action tremor. Six of eight ET patients had complete tremor arrest, and the violent action tremor in all three patients with MS was improved. One patient developed transient arm weakness. Stereotactic radiosurgery for ET and MS-related tremor is safe and effective for patients who may be poor candidates for other procedures.

A comparison of surgical approaches for the management of tremor: radiofrequency thalamotomy, gamma knife thalamotomy and thalamic stimulation.
Niranjan A, Jawahar A, Kondziolka D, Lunsford LD.

Department of Neurological Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA 15213, USA.

OBJECTIVE
Between April 1994 and January 1999, 39 stereotactic procedures for patients with intractable tremor were performed at the University of Pittsburgh Medical Center. A retrospective analysis of results of radiosurgical thalamotomy (n = 15), MR-guided stereotactic radiofrequency thalamotomy (n = 13), and deep brain thalamic stimulation (DBS; n = 11) was performed to study relative advantages and risks of these procedures.

METHODS
All options were discussed with the patients, but radiosurgery usually was performed in elderly patients with concurrent medical problems. Stereotactic thalamotomy and DBS was performed with MR guidance and macrostimulation. For radiosurgery, a median dose of 140 Gy (range 130-150 Gy) was delivered using a single 4-mm collimator.

RESULTS
Of the 13 patients who underwent radiofrequency thalamotomy, 5 had immediate complete arrest of tremor, 6 had a significant reduction and 2 had partial reduction. All 11 patients
who underwent DBS had excellent control of tremor immediately after the procedure, and in longer-term follow-up 10/11 maintained excellent tremor control. Of the 12 evaluable radiosurgery patients, 10 noted excellent relief and 2 had partial relief.

CONCLUSION
Stereotactic procedures for tremor control are safe and effective. Each procedure has specific advantages and disadvantages that are important for patient selection.

Stereotactic radiosurgical pallidotomy and thalamotomy with the gamma knife: MR imaging findings with clinical correlation—preliminary experience.
Friedman DP, Goldman HW, Flanders AE, Gollomp SM, Curran WJ Jr.

Source
Department of Radiology, Wills Eye Hospital, Philadelphia, PA, USA. friedm11@jeclin.tju.edu

Abstract
PURPOSE
To evaluate the temporal evolution and appearance of a radiosurgical lesion at magnetic resonance (MR) imaging and the clinical response in patients undergoing stereotactic radiosurgical pallidotomy or thalamotomy with the gamma knife.

MATERIALS AND METHODS
Seventeen patients with medically refractory movement disorders underwent stereotactic radiosurgical pallidotomy (n = 2) or thalamotomy (n = 15). A single dose of 120-140 Gy was administered to a target in the globus pallidus interna or ventralis intermedius thalamic nucleus. Postprocedure gadolinium-enhanced MR imaging and clinical assessment were performed at 1 month and 3 months.

RESULTS
At 3 months, the radiosurgical lesion most commonly (n = 11) appeared as a ring-enhancing focus 5 mm or less in diameter surrounded by vasogenic edema that extended less than 7 mm in radius beyond the target. Five patients had ring-enhancing lesions 7 mm or more in diameter; four of these developed symptomatic perilesional edema at 3 (n = 2) or 8 (n = 2) months after the procedure. Onset of therapeutic effect began approximately 4 weeks after treatment. In the 15 patients with tremor, there was a mean decline of 2.1 on the Tremor Rating Scale.

CONCLUSION
Findings in this pilot study suggest that radiosurgical thalamotomy is a promising treatment for medically refractory tremor. Three-month follow-up MR studies show a ring-enhancing lesion
surrounded by a variable amount of vasogenic edema. Visualization of the radiosurgical lesion and the clinical response are delayed compared to that with radio-frequency procedures.

**Neurosurg Clin N Am. 1999 Apr;10(2):379-89.**
The treatment of movement disorders using Gamma Knife stereotactic radiosurgery.
Duma CM, Jacques D, Kopyov OV.

Hoag/University of California Irvine Gamma Knife Program, Department of Neurosurgery, Hoag Memorial Hospital Presbyterian, Newport Beach, California 92663, USA.

**Abstract**
In this era of modern neurosurgery, we are able to provide adequate amelioration of disabling symptoms for the small subset of patients who have conditions that may make them unacceptable candidates for invasive stereotactic neurosurgical intervention. Gamma Knife radiosurgical thalamotomy is an effective and useful alternative to invasive radiofrequency techniques for patients at high surgical risk. The mechanical accuracy of the gamma unit combined with the anatomical accuracy of high-resolution magnetic resonance imaging makes radiosurgical lesioning safe and precise.

**J Neurosurg. 1998 Aug;89(2):183-93.**
Gamma knife radiosurgery as a lesioning technique in movement disorder surgery.
Young RF, Shumway-Cook A, Vermeulen SS, Grimm P, Blasko J, Posewitz A, Burkhart WA, Goiney RC.

Northwest Neuroscience Institute and Gamma Knife Center, Northwest Hospital, Seattle, Washington 98133, USA. ryoung@nwhsea.org

**OBJECT**
To increase knowledge of the safety and efficacy of the use of gamma knife radiosurgery in patients with movement disorders, the authors describe their own experience in this field and include blinded independent assessments of their results.

**METHODS**
Fifty-five patients underwent radiosurgical placement of lesions either in the thalamus (27 patients) or globus pallidus (28 patients) for treatment of movement disorders. Patients were evaluated pre- and postoperatively by a team of observers skilled in the assessment of gait and movement disorders who were blinded to the procedure performed. The observers were not associated with the surgical team and concomitantly and blindly also assessed a group of 11 control patients with Parkinson's disease who did not undergo any surgical procedures. All stereotactic lesions were made with the Leksell gamma unit using the 4-mm secondary collimator helmet and a single isocenter with...
maximum doses from 120 to 160 Gy. **Clinical follow-up evaluation indicated that 88% of patients who underwent thalamotomy became tremor free or nearly tremor free.** Statistically significant improvements in performance were noted in the independent assessments of Unified Parkinson's Disease Rating Scale (UPDRS) scores in the patients undergoing thalamotomy. **Of patients undergoing pallidotomy who had exhibited levodopa-induced dyskinesias, 85.7% had total or near-total relief of that symptom.** Clinical assessment indicated improvements in bradykinesia and rigidity in 64.3% of patients who underwent pallidotomy. Independent blinded assessments did not reveal statistically significant improvements in Hoehn and Yahr scores or UPDRS scores. **On the other hand, 64.7% of patients showed improvements in subscores of the UPDRS, including activities of daily living (58%), total contralateral score (58%), and contralateral motor scores (47%).** Total ipsilateral score and ipsilateral motor scores were both improved in 59% of patients. **One (1.8%) of 55 patients experienced a homonymous hemianopsia 9 months after pallidotomy due to an unexpectedly large lesion. No other complications of any kind were seen.** Neuropsychological test scores that were obtained for the combined pallidotomy and thalamotomy treatment groups preoperatively and at 6 months postoperatively demonstrated an absence of cognitive morbidity. Follow-up neuroimaging confirmed correct lesion location in all patients, with a mean maximum deviation from the planned target of 1 mm in the vertical axis. Measurements of lesions at regular intervals on postoperative magnetic resonance images demonstrated considerable variability in lesion volumes. The safety and efficacy of functional lesions made with the gamma knife appear to be similar to those made with the assistance of electrophysiological guidance with open functional stereotactic procedures.

**CONCLUSIONS**

Functional lesions may be made safely and accurately using gamma knife radiosurgical techniques. The efficacy is equivalent to that reported for open techniques that use radiofrequency lesioning methods with electrophysiological guidance. Complications are very infrequent with the radiosurgical method. The use of functional radiosurgical lesioning to treat movement disorders is particularly attractive in older patients and in those with major systemic diseases or coagulopathies; its use in the general movement disorder population seems reasonable as well.
Gamma knife radiosurgery for thalamotomy in parkinsonian tremor: a five-year experience.
Duma CM, Jacques DB, Kopyov OV, Mark RJ, Copcutt B, Farokhi HK.

Source
The Neurosciences Institute and Department of Radiation Oncology, Good Samaritan Hospital, Los Angeles, California 90017, USA.

Abstract
OBJECT
Certain patients, for example, elderly high-risk surgical patients, may be unfit for radiofrequency thalamotomy to treat parkinsonian tremor. Some patients, when given the opportunity, may choose to avoid an invasive surgical procedure. The authors retrospectively reviewed their experience using gamma knife radiosurgery for thalamotomies in this patient subpopulation: 1) to determine the efficacy of the procedure; 2) to see if there is a dose-response relationship; 3) to review radiological findings of radiosurgical lesioning; and 4) to assess the risks of complications.

METHODS
Radiosurgical nucleus ventralis intermedius thalamotomy using the gamma knife unit was performed to make 38 lesions in 24 men and 10 women (median age 73 years, range 58-87 years) over a 5-year period. A median radiation dose of 130 Gy (range 100-165 Gy) was delivered to 38 nuclei (four patients underwent bilateral thalamotomy) using a single 4-mm collimator following classic anatomical landmarks. Twenty-nine lesions were made in the left nucleus ventralis intermedius thalamus for right-sided tremor. Patients were followed for a median of 28 months (range 6-58 months). Independent neurological evaluation of tremor based on the change in the Unified Parkinson's Disease Rating Scale tremor score was correlated with subjective patient evaluation. Comparison was made between a subgroup of patients in whom "low-dose" lesions were made (range 110-135 Gy, mean 120 Gy) and those in whom "high-dose" lesions were made (range 140-165 Gy, mean 160 Gy) for purposes of dose-response information. Four thalamotomies (10.5%) failed, four (10.5%) produced mild improvement, 11 (29%) produced good improvement, and 10 (26%) produced excellent relief of tremor. In nine thalamotomies (24%) the tremor was eliminated completely. The median time to onset of improvement was 2 months (range 1 week-8 months). Concordance between an independent neurologist's evaluation and that of the patient was statistically significant (p < 0.001). Two patients who underwent unilateral thalamotomy experienced bilateral improvement in their tremor. There were no neurological complications. There was better tremor reduction in the high-dose group than in the low-dose group (p < 0.04).

CONCLUSIONS
Although less effective than other stereotactic techniques, gamma knife radiosurgery for thalamotomy offers tremor control with minimal risk to patients unsuited for open surgery.

**Stereotact Funct Neurosurg. 1996;66 Suppl 1:329-32.**
Stereotactic Gamma thalamotomy for the treatment of parkinsonism.
Pan L, Dai JZ, Wang BJ, Xu WM, Zhou LF, Chen XR.

Department of Neurosurgery, Shanghai Gamma Knife Hospital, Shanghai Medical University, P.R. China.

**Abstract**
From September 1994 to June 1995, eight patients with intractable parkinsonism underwent gamma thalamotomy in our hospital. All of these patients were male, with an average age of 59.3 years. The duration of the disease from initial diagnosis was 2-10 years (mean 6.8 years). All had failed or had serious side effects with antiparkinsonian medicine. Seven cases had tremor-dominant symptoms, while the other had mainly rigidity. Six cases had bilateral symptoms. Computed tomography or magnetic resonance imaging (MRI) was undertaken prior to treatment in all cases to exclude focal brain lesions. Stereotactic MRI was taken with the Leksell frame in place and both T1- and T2-weighted images were obtained. The targets were located in the area of Vim/Voa/Vop based on the Schaltenbrand atlas. In seven cases, two plugged 4-mm-collimator shots were used. The maximum dose was 160 Gy in six cases and 180 Gy in one case. In another case, a single 4-mm-collimator shot was used, and a maximum dose of 160 Gy was delivered to the target center. The border of the internal capsule was outside the 20-30% isodose line. We intended the 50% isodose line to have an oval-shaped region with the use of two shots and should correspond to the shape of Vim. Follow-up data were available for six patients (mean: 4.5 months, range: 2-9 months). Tremor disappeared in three cases and improved in the other three. In one of these six cases, the tremor disappeared just 3 days after gamma thalamotomy. Rigidity improved in four of these six cases. In only one patient, treated with a maximum dose of 180 Gy, was there any contralateral limb weakness, which developed 3 months after treatment and has been recovering gradually. Follow-up MRI T2-weighted images in this case showed that the diameter of the lesion was larger than intended and there was a region of diffuse edema in the thalamus and upper brain stem. No other complications occurred in this series.

**Neurol Res. 1995 Feb;17(1):59-65.**
Technique of stereotactic medial thalamotomy with the Leksell Gamma Knife for treatment of chronic pain.
Young RF, Jacques DS, Rand RW, Copcutt BC, Vermeulen SS, Posewitz AE.

Northwest Neuroscience Institute, Seattle, WA, USA.

**Abstract**
Nineteen patients underwent a total of 24 medial thalamic lesions made with the Leksell Gamma Knife for the treatment of chronic intractable pain after extensive prior medical and surgical intervention had failed to provide pain relief. The lesion locations were based on prior experience with open radiofrequency medial thalamotomies for the treatment of pain and were directed at the intralaminar, mediodorsal, centromedian, and parafascicular nuclei. All lesions were made with the 4 mm collimator helmet at radiosurgical doses from 140-180 Gray. Follow-up MRI scans indicated anatomically distinct lesions which developed 3-6 weeks after the procedure and were fully formed by 8-12 weeks. The lesion volumes averaged 300-400 mm$^3$ for a single isocentre, 600-900 mm$^3$ for two isocentres, and 900-1100 mm$^3$ for three isocentres. One patient developed a lesion 5500 mm$^3$ in volume after a two isocentre lesion at 160 Gray. Of 15 patients who have been followed for more than 3 months (average follow-up 12 months) four patients (27%) are virtually pain free and functioning normally, whereas five other patients (33%) achieved greater than 50% pain relief. Thus 9/15 patients (60%) have had worthwhile benefit from medial thalamotomy with the Gamma Knife. Medial thalamotomy with the Gamma Knife produces thalamic lesions which are reliable in size, shape and location with a low complication rate and offers a minimally invasive, cost effective treatment for certain selected patients with chronic intractable pain.


Thalamotomy and caudatotomy with the Gamma Knife as a treatment for parkinsonism with a comment on lesion sizes.
Friehs GM, Ojakangas CL, Pachatz P, Schröttner O, Ott E, Pendl G.

Department of Neurosurgery, University of Graz, Austria.

Abstract
Radiosurgery with the Gamma Knife was performed in 12 patients with parkinsonism. In 9 patients small lesions were created in the head of the caudate nucleus bilaterally. Two patients underwent radiosurgical thalamotomy, and 1 patient was treated with caudatotomy and thalamotomy. After a follow-up period of 1-12 months, 9 patients of the caudatotomy group and all patients with thalamotomies showed clear benefit. There was no complication or side effect that could be related to the treatment. Pre- and postoperative testing was performed with the Unified Parkinson Rating Scale and with objective motor tasks. Caudatotomy proved to be an effective treatment for bradykinesia and rigidity, while tremor was ameliorated by thalamotomy. Functional neurosurgery with the Gamma Knife would seem to be a good alternative to open procedures with low morbidity and no mortality. Advantages and drawbacks of radiosurgical techniques for the treatment of parkinsonism are discussed.
9. Trigeminal neuralgia

Trigeminal neuralgia is a disorder of the fifth cranial (trigeminal) nerve that causes sudden bursts of intense, stabbing, electric shock-like facial pain. The pain is located in the areas supplied by the trigeminal nerve in the face: the cheeks, jaw, teeth, gums and lips and less often around the eye or forehead. These bursts are often triggered by a light touch around the mouth or face or by talking, eating or brushing one's teeth. Usually pain occurs on just one side of the face. The pain responds to Tegretol (carbamazepine), but sometimes the dose has to be increased and unpleasant side effects can occur.

Some patients have very mild face pain that may disappear without treatment. For severe pain, medication, especially Tegretol (carbamazepine), is often highly effective. Tegretol can cause many side effects including sleepiness, forgetfulness, confusion, drowsiness, dizziness and nausea. There are other medications that can be used either alone or in combination to control trigeminal neuralgia pain. They include Lioresal (baclofen), Dilantin (phenytoin), Klonopin (clonazepam), Neurontin (gabapentin) and Lamictal (lamotrigine).

A surgical procedure is recommended for patients who continue to experience severe pain or side effects from medication. There are five important neurosurgical procedures. Each is effective, but not always, and the procedure occasionally has to be repeated. These procedures are: Gamma Knife radiosurgery (GKRS), radiofrequency electrocoagulation (RFE), glycerol injection (GLY), balloon microcompression (BMC) and microvascular decompression (MVD). Some of the procedures treat the nerve at the skull base (GLY, RFE, BMC), while the other procedures treat trigeminal neuralgia at the origin, close to the brain stem where the nerve is irritated by a closely related vessel. This irritation causes the nerve to react with attacks of extreme pain.

The neurosurgical operation MVD is often effective and is generally recommended when the general condition of the patients allows an invasive neurosurgical intervention. MVD treats trigeminal neuralgia at its origin, where an artery compresses the nerve close to the brain stem.

Gamma Knife radiosurgery achieves similar results without open surgery and without general anesthesia and is the most recent and least invasive neurosurgical treatment for trigeminal neuralgia. It treats the trigeminal nerve, just where it leaves the brain. The treatment does not require general anesthesia, and the patient generally stays in the hospital for less than six hours. Through focal irradiation of the trigeminal nerve close to the brain stem, the facial pain can be treated successfully without impairment of other nerve functions.
A recent study after Gamma Knife radiosurgery with long-term follow-up shows that significant pain relief can be achieved in 73% of patients at 1 year, 65% at 2 years and 41% at 5 years (Kondziolka 2010). Most published series show a similar outcome with significant pain relief in between 73 and 86% of patients after the Gamma Knife intervention (see references below). As a side effect in about 10% of patients, facial sensation may be mildly affected after radiosurgery (facial paresthesias). Gamma Knife treatment is a noninvasive and pain-free procedure performed under local anesthesia. Patients with trigeminal neuralgia who are suffering from severe pain or problems with the medicines used to relieve the pain are potential candidates for Gamma Knife radiosurgery. Patients who have had other previous unsuccessful procedures for trigeminal neuralgia can also undergo Gamma Knife treatment.

Selected Literature 2001-2012: Gamma Knife Radiosurgery for Trigeminal neuralgia

Stereotact Funct Neurosurg. 2012 Apr 11;90(3):145-150. [Epub ahead of print]
Gamma Knife Radiosurgery in the Treatment of Tumor-Related Facial Pain.
Squire SE, Chan MD, Furr RM, Lowell DA, Tatter SB, Ellis TL, Bourland JD, Deguzman AF, Munley MT, Ekstrand KE, Shaw EG, McMullen KP.

Department of Radiation Oncology, Wake Forest University, Winston-Salem, N.C., USA.

BACKGROUND:
Intracranial neoplasms can cause pain similar to trigeminal neuralgia. Literature regarding radiosurgery for this is limited. We present a retrospective review of patients with tumor-related facial pain from benign lesions treated with gamma knife radiosurgery (GKRS) at Wake Forest University.

OBJECTIVES:
The primary objectives were to determine long-term pain relief and predictive factors for pain alleviation.

METHODS:
We reviewed 515 patients treated with GKRS for benign meningioma, vestibular schwannoma or trigeminal schwannoma between August 1999 and August 2010. Twenty-one eligible patients had tumor-related facial pain prior to GKRS. The median marginal tumor dose was 12 Gy. Long-term pain relief data were obtained by chart review and telephone interview.

RESULTS:
The median follow-up for symptom evaluation was 3.8 years. Seventeen of 21 patients (81%) experienced a Barrow Neurological Institute (BNI) score of I-III at 6 months following GKRS. Kaplan-Meier estimates of freedom from BNI IV-V relapse were 66% at 1 year and 53% at 2 years. No pain relapses occurred after 2 years.

CONCLUSION:
GKRS of benign lesions is a noninvasive option for patients with tumor-related facial pain. Pain relief is modest, with the majority of pain relapses occurring within 2 years and approximately one half of patients maintaining relief beyond 2 years.

Clinical outcomes of 114 patients who underwent Gamma-knife radiosurgery for medically refractory idiopathic trigeminal neuralgia.
Li P, Wang W, Liu Y, Zhong Q, Mao B.

Department of Neurosurgery, West China Hospital, Sichuan University, 37 Guoxue Alley, Chengdu 610041, Sichuan Province, China.

The optimal radiation dose and target of Gamma-knife radiosurgery (GKRS) for medically refractory idiopathic trigeminal neuralgia (TN) are contentious. We investigated the effects and trigeminal nerve deficits of GKRS using two isocenters to treat a great length of the trigeminal nerve. Between January 2005 and March 2010, 129 patients with idiopathic TN underwent GKRS at the West China Hospital of Sichuan University. A maximum central dose of 80-90 Gy was delivered to the trigeminal nerve root with two isocenters via a 4mm collimator helmet. One hundred and fourteen patients were followed-up periodically by telephone interview to determine the effects, trigeminal nerve deficits and time to the onset of pain relief. The mean follow-up duration was 29.6 months. One hundred and nine patients had complete or partial pain relief and the treatment failed in five patients. Nine patients experienced a recurrence after a mean time of 12.7 months, following an initial interval of pain relief. The early response to the treatment might suggest a good outcome but, given the high incidence of nerve deficits, GKRS for TN with two isocenters is not recommended as a routine treatment protocol.
Trigeminal neuralgia is characterized by a temporary paroxysmal lancinating facial pain in the trigeminal nerve distribution. The prevalence is four to five per 100,000. Local pressure on nerve fibers from vascular loops results in painful afferent discharge from an injured segment of the fifth cranial nerve. Microvascular decompression addresses the underlying pathophysiology of the disease, making this treatment the gold standard for medically refractory trigeminal neuralgia. In patients who cannot tolerate a surgical procedure, those in whom a vascular etiology cannot be identified, or those unwilling to undergo an open surgery, stereotactic radiosurgery is an appropriate alternative. The majority of patients with typical facial pain will achieve relief following radiosurgical treatment. Long-term follow-up for recurrence as well as for radiation-induced complications is required in all patients undergoing stereotactic radiosurgery for trigeminal neuralgia.

Stereotactic radiosurgery is one of a number of recognised treatments for the management of trigeminal neuralgia refractory to drug therapy. The reported success of stereotactic radiosurgery in managing patients with trigeminal neuralgia varies in different units from 22 to 75%. This paper reports the outcomes of patients with trigeminal neuralgia who were treated at the National Centre for Stereotactic Radiosurgery in Sheffield, UK. The study reports the outcome of 72 patients treated consecutively between October 2004 and May 2008. Data were collected prospectively by a postal questionnaire sent to patients at 6, 12 and 24 months after treatment. The median age was 65.6 years (39 males: 33 females). Fourteen patients had secondary trigeminal neuralgia (eight multiple sclerosis). Fifteen of the patients included in the study were receiving a second treatment (an initial treatment having improved their pain significantly for at least 6 months). All radiosurgical procedures were performed using a single 4 mm collimator isocenter covering the region of the dorsal root entry zone with a maximal radiation dose of 80 Gy. The percentage of patients defined as having an
excellent outcome (pain free without medication) was 39% after 6 months, 36% after 12 months and 64% after 24 months. The percentage of patients who reported being very satisfied with treatment was 71% after 6 months, 57% after 12 months and 53% after 24 months. Half the patients with secondary trigeminal neuralgia were pain free without medication after treatment, and 60% of patients who underwent a second treatment were pain free. A new trigeminal sensory deficit was reported by 31% of patients after radiosurgical treatment.

Stereotactic radiosurgery of essential trigeminal neuralgia using Leksell Gamma Knife model C with automatic positioning system: technical nuances and evaluation of outcome in 130 patients with at least 2 years follow-up after treatment.
Faculty of Advanced Techno-Surgery, Institute of Advanced Biomedical Engineering and Science, Tokyo Women’s Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, 162-8666, Japan.
GKRmoto@aol.com

The objective of the present study was the evaluation of outcome in 130 patients with essential trigeminal neuralgia, who were treated using Leksell Gamma Knife model C with automatic positioning system and followed at least 24 months thereafter. Radiosurgery was guided by fused thin-sliced magnetic resonance (MR) and "bone window" computed tomographic (CT) images. In all cases, retrogasserian part of the trigeminal nerve at the level of trigeminal incisura was selected as a target, and one 4-mm collimator was used for delivery of the maximum irradiation dose of 90 Gy. The coordinates of the isocenter were adjusted for positioning of the nerve in the center of 80% isodose area, and were corrected in each individual case with regard to presence of distortion artifacts on MR images. Initial relief of the typical paroxysmal facial pain was marked in 127 patients (98%) within a median interval of 3 weeks after treatment. However, in 23 patients the pain re-appeared later on. Overall, at the time of the last follow-up 112 patients (86%) were pain-free, including 86 who remained both pain- and medication-free after initial radiosurgery. In 31 cases (24%), treatment was complicated by facial hypesthesia and/or paresthesia. In conclusion, radiosurgery of essential trigeminal neuralgia results in a high rate of initial pain relief, but pain recurrences and associated complications are not uncommon. The outcome may be influenced by various technical nuances; therefore, treatment should be preferably done in specialized clinical centers with sufficient expertise in the management of this disorder.
**Clin Neurol Neurosurg. 2011 Jul;113(6):447-52. Epub 2011 Feb 16.**

Gamma knife radiosurgery for idiopathic trigeminal neuralgia as primary vs. secondary treatment option.

Park YS, Kim JP, Chang WS, Kim HY, Park YG, Chang JW.

Department of Neurosurgery, Bundang CHA Hospital, CHA University School of Medicine, Seongnam, Korea.

**OBJECTIVE**

To enable physicians to remain informed of secondary GKR after multiple surgical choices. This study compares gamma knife radiosurgery (GKR) as a first and a second treatment for the management of medically refractory idiopathic trigeminal neuralgia (TN).

**METHODS**

Between May 1998 and May 2008, a total of **86 patients with idiopathic TN underwent GKR**, with 62 patients receiving the treatment as a first therapy (primary GKR group) and 24 patients receiving the treatment as a second procedure (secondary GKR group). The median follow-up time was **76.4 months** (range 12-161 months). The mean prescription marginal dose delivered to the involved trigeminal nerve root entry zone was 82.4±6.25Gy for the primary GKR group, and 81.0±4.89Gy for the secondary GKR group. In the secondary group, eleven patients underwent percutaneous radiofrequency rhizotomy (PRFR), seven underwent microvascular decompression (MVD), three underwent percutaneous glycerol rhizotomy and another three underwent GKR as their first treatment. We excluded a typical, multiple sclerosis or secondary trigeminal neuralgia.

**RESULTS**

No significant differences in radiation dose, time to initial response, recurrence or pain relief were observed between the use of GKR as a primary and a secondary procedure for idiopathic TN. The occurrence of new onset after GKR were the same for the two groups, but overall facial sensory changes was higher in the secondary GKR group.

**CONCLUSION**

For pain control, GKR can be offered both as a primary and as a secondary procedure, but shows higher overall facial sensory changes in secondary GKR group. The results of our study enable physicians to remain informed of secondary GKR after multiple surgical choices. GKR would be an alternative treatment modality after other surgical treatments including GKR, MVD, PRFR and Glycerol.
Does the Gamma Knife dose rate affect outcomes in radiosurgery for trigeminal neuralgia?

Department of Neurological Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213, USA.

OBJECT
The object of this study was to determine whether the radiation dose rate affects clinical outcomes in patients who undergo stereotactic Gamma Knife surgery (GKS) to manage typical trigeminal neuralgia (TN).

METHODS
The authors retrospectively studied pain relief in 165 patients with medically intractable TN, who underwent 80-Gy GKS using a single 4-mm collimator between 1994 and 2005. No patient had received prior radiation treatment. The measured relative helmet output factor of the Gamma Knife was 0.8 throughout this interval, and the dose rate varied from 1.21 Gy/minute to 3.74 Gy/minute (median 2.06 Gy/minute). Irradiation time varied from 26.73 to 95.11 minutes. The authors divided patients into a low-dose-rate (LDR) group, in which the dose rate varied from 1.21 to 2.05 Gy/minute, and a high-dose-rate (HDR) group, in which the dose rate varied from 2.06 to 3.74 Gy/minute. Post-GKS, the patients' pain control was determined using the Barrow Neurological Institute (BNI) pain scale. There was no statistically significant difference between groups with respect to history of prior microvascular decompression (p = 0.410) or peripheral neuroablative procedures (p = 0.583). The length of symptoms in patients varied from 3 to 414 months with a median of 84 months (p = 0.698). Median follow-up was 26 months with a maximum of 139 months.

RESULTS
Initial pain relief was obtained in 71% of patients in the LDR group and 78% in the HDR group (p = 0.547). Patients who initially obtained improved pain relief (BNI Scores I-IIIa) after GKS maintained pain control for median durations of 52 months (LDR group) and 54 months (HDR group) (p = 0.403). New or increased facial sensory dysfunction was found in 14.5% of patients in the LDR group and in 19.3% of patients in the HDR group (p = 0.479).

CONCLUSIONS
The authors found that the GKS dose rate did not affect pain control or morbidity within the range of 1.21-3.74 Gy/minute. Cobalt 60 source decay did not affect outcomes of GKS for TN pain management, even for dose rates approximating a 2-half-life decay of the isotope.
Gamma Knife surgery for trigeminal neuralgia: a review of 450 consecutive cases.

Verheul JB, Hanssens PE, Lie ST, Leenstra S, Piersma H, Beute GN.

Gamma Knife Center Tilburg, Sint Elisabeth Hospital, Tilburg, The Netherlands. j.verheul@elisabeth.nl

OBJECT
The success rates and side effects of Gamma Knife surgery (GKS) in patients with trigeminal neuralgia (TN) are not fully clear. A comparison of data across previous reports is hampered by differences in treatment protocols, lengths of follow-up, and outcome criteria. The purpose of this paper is to contribute to knowledge of the efficacy of GKS in TN by reviewing data in a large group of patients with this disorder, who were treated with a uniform treatment protocol and evaluated using a well-established pain scale and Kaplan-Meier analysis.

METHODS
The authors reviewed 450 treatments in 365 patents with medically refractory TN who were treated between June 2002 and October 2009 at the Gamma Knife Center Tilburg. In all patients 80 Gy was prescribed, with a single 4-mm isocenter located at the root entry zone (REZ). In 79 patients repeated GKS was performed using a uniform dose of 80 Gy, which was delivered, in a highly standardized manner, to a spot anterior to the position of the first treatment. Follow-up was obtained by reviewing the patients' medical records and conducting telephone interviews. Outcome was assessed using the Barrow Neurological Institute (BNI) pain scale and the BNI facial numbness scale.

RESULTS
The median follow-up period was 28 months. In the idiopathic TN group, rates of adequate pain relief, defined as BNI Pain Scores I-IIIB, were 75%, 60%, and 58% at 1, 3, and 5 years, respectively. In the multiple sclerosis (MS)-related TN group the rates of adequate pain relief were 56%, 30%, and 20% at 1, 3, and 5 years, respectively. Repeated GKS was as successful as the first. An analysis of our treatment strategy of repeated GKS showed rates of adequate pain relief of 75% at 5 years in the idiopathic TN and 46% in the MS-related TN group. Somewhat bothersome numbness was reported by 6% of patients after the first treatment and by 24% after repeated GKS. Very bothersome numbness was reported in 0.5% after the first GKS and in 2% after the second treatment.

CONCLUSIONS
In this study the authors analyzed outcomes of GKS in a large cohort of patients with TN; uniform treatment consisted of 80 Gy delivered to the REZ. The initial and long-term outcomes of pain relief and sensory dysfunction are comparable to recently published results at other institutions, where similar
outcome criteria were used. These data should prove helpful to assist patients and clinicians in their TN management decisions.

Neurosurgery. 2010 Dec;67(6):1637-44; discussion 1644-5.
Outcome predictors after gamma knife radiosurgery for recurrent trigeminal neuralgia.
Kano H, Kondziolka D, Yang HC, Zorro O, Lobato-Polo J, Flannery TJ, Flickinger JC, Lunsford LD.

Department of Neurological Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213, USA.

BACKGROUND
Trigeminal neuralgia (TN) that recurs after surgery can be difficult to manage.

OBJECTIVE
To define management outcomes in patients who underwent gamma knife stereotactic radiosurgery (GKSR) after failing 1 or more previous surgical procedures.

METHODS
We retrospectively reviewed outcomes after GKSR in 193 patients with TN after failed surgery. The median patient age was 70 years (range, 26-93 years). Seventy-five patients had a single operation (microvascular decompression, n=40; glycerol rhizotomy, n=24; radiofrequency rhizotomy, n=11). One hundred eighteen patients underwent multiple operations before GKSR. Patients were evaluated up to 14 years after GKSR.

RESULTS
After GKSR, 85% of patients achieved pain relief or improvement (Barrow Neurological Institute grade I-IIIb). Pain recurrence was observed in 73 of 168 patients 6 to 144 months after GKSR (median, 6 years). Factors associated with better long-term pain relief included no relief from the surgical procedure preceding GKSR, pain in a single branch, typical TN, and a single previous failed surgical procedure. Eighteen patients (9.3%) developed new or increased trigeminal sensory dysfunction, and 1 developed deafferentation pain. Patients who developed sensory loss after GKSR had better long-term pain control (Barrow Neurological Institute grade I-IIIb: 86% at 5 years).

CONCLUSION
GKSR proved to be safe and moderately effective in the management of TN that recurs after surgery. Development of sensory loss may predict better long-term pain control. The best candidates for GKSR were patients with recurrence after a single failed previous operation and those with typical TN in a single trigeminal nerve distribution.
Outcomes following single-treatment Gamma Knife surgery for trigeminal neuralgia with a minimum 3-year follow-up.


Boston Gamma Knife Center at Tufts Medical Center, Boston, Massachusetts, USA.

OBJECT

Gamma Knife surgery (GKS) has been shown to be effective in treating trigeminal neuralgia (TN). Existing studies have demonstrated success rates of 69.1-85% with median follow-up intervals of 19-60 months. However, series with uniform long-term follow-up data for all patients have been lacking. In the present study the authors examined outcomes in a series of patients with TN who underwent a single GKS treatment followed by a minimum follow-up of 36 months. They used a clinical scale that simplifies the reporting of outcome data for patients with TN.

METHODS

Fifty-three consecutive patients with typical, intractable TN received a median maximum radiation dose of 80 Gy applied with a single 4-mm isocenter to the affected trigeminal nerve. Follow-up data were obtained by clinical examination and questionnaire. Outcome results were categorized into the following classes (in order of decreasing success): Class 1A, complete pain relief without medications; 1B, complete pain relief with either a decrease or no change in medications; 1C, > or = 50% pain relief without medications; 1D, > or = 50% pain relief with either a decrease or no change in medications; and Class 2, < 50% pain relief and/or increase in medications. Patients with Class 1A-1D outcome (equivalent to Barrow Neurological Institute Grades I-IIIb) were considered to have a good treatment outcome, whereas in patients with Class 2 outcome (equivalent to Barrow Neurological Institute Grades IV and V) treatment was considered to have failed.

RESULTS

A good treatment outcome from initial GKS was achieved in 31 (58.5%) patients for whom the mean follow-up period was 48 months (range 36-66 months). Outcomes at last follow-up were reflected by class status: Class 1A, 32.1% of patients; 1B, 1.9%; 1C, 3.8%; 1D, 20.8%; and Class 2, 41.5%. Statistical analysis showed no difference in outcomes between patients previously treated with microvascular decompression or rhizotomy compared with patients with no previous surgical treatments. Thirty-six percent of patients reported some degree of posttreatment facial numbness. Anesthesia dolorosa did not develop in any patient.

CONCLUSIONS
Despite a time-dependent deterioration in the success rate of GKS for medically intractable TN, the authors' study showed that > 50% of patients can be expected to have a good outcome based on their scoring system, with approximately 33% having an ideal outcome (pain free with no need for medications). Long-term data, as those presented here, are important when counseling patients on their treatment options.

**Neurochirurgie. 2009 Apr;55(2):213-22. Epub 2009 Apr 1.**

[Radiosurgery in trigeminal neuralgia: long-term results and influence of operative nuances].
[Article in French]

Service de neurochirurgie fonctionnelle et stéréotaxique, hôpital de la Timone, 13385 Marseille cedex 05, France. jregis@ap-hm.fr

Stereotactic radiosurgery is an alternative to conventional surgery for the treatment of trigeminal neuralgia. To better define the safety of radiosurgery and optimal technical choices, we reviewed our patient records and the literature. A total of 334 patients presenting with trigeminal neuralgia were treated between December 1992 and September 2005. A minimum of 1 year of follow-up was available for 262 patients. The mean age was 68 years (range: 30-90); 128 patients were male and 134 female. A neurovascular conflict was clearly visualized on MRI in 167 patients. Twenty-one had a past history of multiple sclerosis and 110 had already received conventional surgical treatment for trigeminal neuralgia. The intervention consisted of gamma knife radiosurgery (GKS) to the retrogasserian cisternal portion of the Vth cranial nerve. The median maximal dose used was 85Gy (range: 70-90). Actuarial curves show a plateau at 5 years for both the risk of hypoesthesia and recurrence. At 5 years, 58% of the patients remain pain-free and 83% have no trigeminal nerve disturbance. The median delay for pain cessation was 15 days. The initial pain-relief rate was 89%. None of the complications reported for the other techniques were observed. Patient selection (typical versus atypical, age, past surgery, multiple sclerosis) and details of operative technique (maximum dose, volume of nerve treated, target location, etc.) had a major influence on the probability of pain relief and toxicity risk. The details of operative technique are turning out to have a major influence on the clinical results. In our experience, high-dose (80-90Gy) retrogasserian (7-8mm from the brainstem) GKS provides the patient with a better chance of long-term pain relief and a lower risk of trigeminal nerve functional disturbance. GKS applied to the cisternal anterior trigeminal nerve using high doses provided safe and effective treatment for trigeminal neuralgia over the long term.
Trigeminal neuralgia: outcomes after gamma knife radiosurgery.

Knafo H, Kenny B, Mathieu D.

Division of Neurosurgery/Radiosurgery, Department of Surgery, Centre Hospitalier Universitaire de Sherbrooke, Université de Sherbrooke, Sherbrooke, Quebec, Canada.

BACKGROUND

Trigeminal neuralgia (TN) often remains difficult to treat despite multiple available medications, and can severely impact on the quality of life of affected patients. Gamma knife radiosurgery has recently emerged as a minimally-invasive alternative to surgery for patients suffering from drug-resistant TN. The goal of this study was to report the short-term efficacy of gamma knife radiosurgery for TN and assess its impact on the quality of life of patients treated in the first 18 months of our experience.

METHODS

Patients with medically-refractory TN or with unacceptable drug side effects were considered for radiosurgery. A maximum dose of 80 Gy was administered to the affected nerve using a single 4-mm isocenter. Follow-up assessments were made at 2, 4 and 6 months, with evaluation of pain relief, drug reduction and quality of life. Factors impacting treatment response were assessed using Cox regression analysis.

RESULTS

A total of 67 patients were treated. Significant pain relief was seen in 77.6% of patients, including 32.6% who became pain-free. Patients were able to discontinue all medications in 34.3% or reduce drug intake by more than 50% in an additional 28.4% of cases. No variable was found to predict pain relief although older age (>66 years) approached statistical significance. Sensory side effects were seen in 14.9% of patients. Quality of life improved in the majority of patients after radiosurgery.

CONCLUSIONS

Gamma knife radiosurgery is a safe and effective management alternative for trigeminal neuralgia, providing good or excellent pain relief and improvement in quality of life in the majority of patients with few side effects.
OBJECT
Gamma Knife surgery (GKS) is an effective treatment for intractable trigeminal neuralgia (TN). The authors compared results using two major GKS target points, the dorsal root entry zone and the retrogasserian portion, in a series of patients with intractable TN.

METHODS
One hundred patients with medically refractory TN underwent GKS between August 1998 and December 2007. Thirty-seven were men, and 63 were women. The median age at GKS was 74 years. With a single isocenter and use of a 4mm collimator, 51 patients received 80 Gy at the proximal trigeminal nerve (posterior group) and 7 patients received 80 Gy, 1 patient received 85 Gy, and 41 patients received 90 Gy at the retrogasserian portion (anterior group). Follow-up was obtained by clinic visits every 3-6 months after GKS. Data on pain control, complications, and pain recurrence were recorded. The relationships between pain control status, complications, recurrence, and the target portions (anterior vs posterior) were analyzed.

RESULTS
The median duration of follow-up was 30 months (range 3-88 months). Initially, 87 patients achieved pain-free status and 64 achieved complete remission. At the final follow-up visit, 68 patients were still in pain-free status and 42 were in complete remission. Recurrence of facial pain occurred in 15 patients. Forty-one patients developed some degree of trigeminal dysfunction. The rate of initial complete remission was higher in the posterior group than in the anterior group \( (p = 0.003) \). More complications were observed in the anterior group than in the posterior group \( (p = 0.009) \).

CONCLUSIONS
The posterior targeting group had better pain control and a lower complication rate. The authors recommend the posterior targeting method and use of 80 Gy for treatment of TN with GKS.

Linskey ME, Ratanatharathorn V, Peñagaricano J.

Department of Neurological Surgery, University of California, Irvine Medical Center, Orange, California 92868, USA. mlinskey@uci.edu

OBJECT
The aim of this study was to analyze 1 surgeon’s 4-year experience with microvascular decompression ([MVD], 36 patients) and Gamma Knife surgery ([GKS], 44 patients) in 80 consecutive patients with trigeminal neuralgia (TN).

METHODS
The authors conducted a prospective cohort study from March 1999 to December 2003 with an independent clinical assessment of the results and serial patient satisfaction surveys. All patients completed a 2004 patient satisfaction survey (0.5-5 years postoperative), and 70% of surviving patients completed the same survey in 2007 (3.9-8.5 years postoperative). Follow-up was undertaken in 100% of the patients (mean 3.4 +/- 2.14 years, range 0.17-8.5 years).

RESULTS
Respective initial and latest follow-up raw pain-free rates were 100 and 80.6% for MVD and 77.3 and 45.5% for GKS. The median time to the maximal benefit after GKS was 4 weeks (range 1 week-6 months). Respective initial, 2-, and 5-year actuarial pain-free rates were 100, 88, and 80% for MVD and 78, 50, and 33% for GKS (p = 0.0002). The relative risk of losing a pain-free status by 5 years posttreatment was 3.35 for patients in the GKS group compared with the MVD group. Initial and 5-year actuarial rates for >or= 50% pain relief after GKS were 100 and 80%, respectively. The respective rates of permanent mild and severe sensory loss were 5.6 and 0% for patients in the MVD group, as opposed to 6.8 and 2.3% for patients in the GKS group. Anesthesia dolorosa did not occur during the study. Both procedures enjoyed a high degree of early patient satisfaction (95-100%). Microvascular decompression maintained the same rate of patient satisfaction, but satisfaction with GKS decreased to 75% as pain control waned. Twenty-three patients (29%) died of causes unrelated to the TN or the surgical intervention during the follow-up, and their pain status was known at the time of death. Statistically significant intergroup differences for the MVD versus GKS cohorts were age (median 54 years, range 36-70 years vs median 74 years, range 48-92 years, respectively), preoperative symptom duration (median 2.58 years, range 0.33-15 years vs median 7.5, range 0.6-40 years, respectively), and the presence of major comorbidities (2.8 vs 58.3%, respectively).

CONCLUSIONS
In this nonrandomized prospective cohort trial of selected patients with potentially relevant intergroup differences, MVD was significantly superior to GKS in achieving and maintaining a pain-free status in those with TN and provided similar early and superior longer-term patient satisfaction rates compared with those for GKS. The complications of wound cerebrospinal fluid leakage, hearing loss, and persistent diplopia (1 case each in the MVD group) were not seen after GKS.

The Treatment Outcome of Elderly Patients with Idiopathic Trigeminal Neuralgia: Micro-Vascular Decompression versus Gamma Knife Radiosurgery.
Oh IH, Choi SK, Park BJ, Kim TS, Rhee BA, Lim YJ.
Department of Neurosurgery, Kyung Hee University Hospital, Seoul, Korea.

OBJECTIVE
This study was designed to compare the efficacy of micro-vascular decompression (MVD) and Gamma knife radiosurgery (GKRS) for elderly idiopathic trigeminal neuralgia patients by analyzing the clinical outcome.

METHODS
In the past 10 years, 27 elderly patients were treated with MVD while 18 patients were treated with GKRS (>65-years-old). We reviewed their clinical characteristics and clinical courses after treatment as well as the treatment outcomes. For patients who were treated with MVD, additional treatment methods such as rhizotomy were combined in some areas. In GKRS, we radiated the root entry zone (REZ) with the mean maximum dose of 77.8 (70-84.3) Gy and one 4 mm collimator.

RESULTS
The mean age was 68.1 years for MVD, and 71.1 years for GKS group. The average time interval between first presenting symptom and surgery was 84.1 (1-361) months, and 51.4 (1-120) months, respectively. The mean follow-up period after the surgery was 35.9 months for MVD, and 33.1 months for GKRS. According to Pain Intensity Scale, MVD group showed better prognosis with 17 (63%) cases in grade I-II versus 10 (55.6%) cases in GKRS group after the treatment. The pain recurrence rate during follow up did not show much difference with 3 (11.1%) in MVD, and 2 (11.1%) in GKRS. After the treatment, 2 cases of facial numbness, and 1 case each of herpes zoster, cerebrospinal fluid (CSF) leakage, hearing disturbance, and subdural hematoma occurred in MVD Group. In GKRS, there was 1 (5.6%) case of dysesthesia but was not permanent. Three cases were retreated by GKRS but the prognosis was not as good as when the surgery was used as primary treatment, with 1 case of grade I-II, and 1 case of recurrence. The maximal relieve of pain was seen just after surgery in MVD group, and 1 year after treatment in GKRS group.
CONCLUSION
For trigeminal neuralgia patients with advanced age, MVD showed advantages in immediately relieving the pain. However, in overall, GKRS was preferable, despite the delayed pain relief, due to the lower rate of surgical complications that arise owing to the old age.

Long-term pain response and quality of life in patients with typical trigeminal neuralgia treated with gamma knife stereotactic radiosurgery.
Little AS, Shetter AG, Shetter ME, Bay C, Rogers CL.
Division of Neurosurgery, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, Arizona 85013, USA.

OBJECTIVE
The long-term outcome of patients treated with gamma knife radiosurgery (GKRS) for typical trigeminal neuralgia has not been fully studied. We evaluated 185 patients who underwent their first GKRS treatment between 1997 and 2003 at the Barrow Neurological Institute.

METHODS
Follow-up was obtained by surveys and review of medical records. Outcomes were assessed by the Barrow Neurological Institute Pain Intensity Score and Brief Pain Inventory. The most common maximum dose was 80 Gy targeted at the root entry zone. Outcomes are presented for the 136 (74%) patients for whom more than 4 years of clinical follow-up data were obtained.

RESULTS
Treatment failed in 33% of the cohort within 2 years, but only an additional 1% relapsed after 4 years. Actuarial analysis demonstrated that 32% of patients were pain-free off medication and 63% had at least a good outcome at 7 years. When GKRS was used as the primary treatment, 45% of the patients were pain-free at 7 years. In contrast, 10% of patients in whom previous treatment had failed were pain-free. When needed, salvage therapy with repeat GKRS, microvascular decompression, or percutaneous lesioning was successful in 70%. Posttreatment facial numbness was reported as very bothersome in 5%, most commonly in patients who underwent another invasive treatment. After GKRS, 73% reported that trigeminal neuralgia had no impact on their quality of life.

CONCLUSION
GKRS is a reasonable long-term treatment option for patients with typical trigeminal neuralgia. It yields durable pain control in a majority of patients, as well as improved quality of life with limited
complications and it does not significantly affect the efficacy of other surgical treatments, should they be needed.


Practice parameter: the diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the European Federation of Neurological Societies.


American Academy of Neurology, 1080 Montreal Avenue, St. Paul, MN55116, USA. guidelines@aan.com

**BACKGROUND**

Trigeminal neuralgia (TN) is a common cause of facial pain.

**PURPOSE**

To answer the following questions: 1) In patients with TN, how often does routine neuroimaging (CT, MRI) identify a cause? 2) Which features identify patients at increased risk for symptomatic TN (STN; i.e., a structural cause such as a tumor)? 3) Does high-resolution MRI accurately identify patients with neurovascular compression? 4) Which drugs effectively treat classic and symptomatic trigeminal neuralgia? 5) When should surgery be offered? 6) Which surgical technique gives the longest pain-free period with the fewest complications and good quality of life?

**METHODS**

Systematic review of the literature by a panel of experts.

**CONCLUSIONS**

In patients with trigeminal neuralgia (TN), routine head imaging identifies structural causes in up to 15% of patients and may be considered useful (Level C). Trigeminal sensory deficits, bilateral involvement of the trigeminal nerve, and abnormal trigeminal reflexes are associated with an increased risk of symptomatic TN (STN) and should be considered useful in distinguishing STN from classic trigeminal neuralgia (Level B). There is insufficient evidence to support or refute the usefulness of MRI to identify neurovascular compression of the trigeminal nerve (Level U). Carbamazepine (Level A) or oxcarbazepine (Level B) should be offered for pain control while baclofen and lamotrigine (Level C) may be considered useful. **For patients with TN refractory to medical therapy, Gasserian ganglion percutaneous techniques, gamma knife, and microvascular decompression may be considered (Level C).** The role of surgery vs pharmacotherapy in the management of TN in patients with MS remains uncertain.
Neurosurgery. 2007 Dec;61(6):1254-60; discussion 1260-1.
Gamma knife radiosurgery for trigeminal neuralgia: results and potentially predictive parameters--part I: Idiopathic trigeminal neuralgia.
Longhi M, Rizzo P, Nicolato A, Foroni R, Reggio M, Gerosa M.
Department of Neurosurgery, University Hospital, Verona, Italy.

OBJECTIVE
Gamma knife radiosurgery (GKR) is an increasingly used, minimally invasive treatment option for patients with trigeminal neuralgia (TN) refractory to medical therapy. This retrospective study evaluates the long-term results and side effects of GKR in the treatment of TN focusing on potentially predictive factors.

METHODS
One hundred sixty patients with TN were included in this study (minimum follow-up, >6 mo; mean, 37.4 mo; range, 6-144 mo). In 92 patients, GKR represented the first nonmedical option ("primary GKR"). In 68 patients, invasive treatments had been previously attempted. All patients were treated using a single 4-mm collimator shot targeting the pontine trigeminal root entry zone with a maximal dose of 75 to 95 Gy. Brainstem dose exposure never exceeded 15 Gy. Treatment outcome results were classified as Grade I (pain-free with no pharmacological treatment), Grade II (pain-free with pharmacological treatment), and Grade III (no result). Data were analyzed using the log-rank test for univariate analysis and the ordered logit model for multivariate analysis.

RESULTS
In the overall series, 98 (61%) out of 160 patients reached a Grade I outcome, 45 (29%) reached a Grade II outcome, and 17 (10%) patients had no results from GKR. These results were encouraging for patients with typical facial pain features and for patients treated by a "primary" gamma knife. Considering the global outcome, the most effective and safest dose was found to be in the 80 to 90 Gy range.

CONCLUSION
According to our experience, GKR represents a reliable second-line therapeutic approach for TN after pharmacological failure. Favorable prognostic factors include "primary GKR" and maximal GKR dose ranging between 80 and 90 Gy.
Clinical evaluation of targeting accuracy of gamma knife radiosurgery in trigeminal neuralgia.

Massager N, Abeloos L, Devriendt D, Op de Beeck M, Levivier M.

Gamma Knife Center and Department of Neurosurgery, University Hospital Erasme, Université Libre de Bruxelles, Brussels, Belgium. nmassage@ulb.ac.be

PURPOSE
The efficiency of radiosurgery is related to its highly precise targeting. We assessed clinically the targeting accuracy of radiosurgical treatment with the Leksell Gamma Knife for trigeminal neuralgia. We also studied the applied radiation dose within the area of focal contrast enhancement on the trigeminal nerve root following radiosurgery.

METHODS AND MATERIALS
From an initial group of 78 patients with trigeminal neuralgia treated with gamma knife radiosurgery using a 90-Gy dose, we analyzed a subgroup of 65 patients for whom 6-month follow-up MRI showed focal contrast enhancement of the trigeminal nerve. Follow-up MRI was spatially coregistered to the radiosurgical planning MRI. Target accuracy was assessed from deviation of the coordinates of the intended target compared with the center of enhancement on postoperative MRI. Radiation dose delivered at the borders of contrast enhancement was evaluated.

RESULTS
The median deviation of the coordinates between the intended target and the center of contrast enhancement was 0.91 mm in Euclidean space. The radiation doses fitting within the borders of the contrast enhancement of the trigeminal nerve root ranged from 49 to 85 Gy (median value, 77 +/- 8.7 Gy).

CONCLUSIONS
The median deviation found in clinical assessment of gamma knife treatment for trigeminal neuralgia is low and compatible with its high rate of efficiency. Focal enhancement of the trigeminal nerve after radiosurgery occurred in 83% of our patients and was not associated with clinical outcome. Focal enhancement borders along the nerve root fit with a median dose of 77 +/- 8.7 Gy.
Does dose rate affect efficacy? The outcomes of 256 gamma knife surgery procedures for trigeminal neuralgia and other types of facial pain as they relate to the half-life of cobalt.

OBJECT

Gamma Knife surgery (GKS) is a treatment option for patients with refractory typical trigeminal neuralgia (TN), TN with atypical features, and atypical types of facial pain. The Gamma Knife's 201 60Co sources decay with a half-life of 5.26 years. The authors examined whether the decrease in dose rate over 4.6 years between Co source replacements affected the control rates of facial pain in patients undergoing GKS.

METHODS

The authors collected complete follow-up data on 239 of 326 GKS procedures performed in patients with facial pain. Patients were classified by their type of pain. The isocenter of a 4-mm collimator helmet was targeted at the proximal trigeminal nerve root, and the dose (80-90 Gy) was prescribed at the 100% isodose line. Patients reported the amount of pain control following radiosurgery by answering a standardized questionnaire. Eighty percent of patients experienced greater than 50% pain relief, and 56% of patients experienced complete pain relief after GKS. Neither dose rate nor treatment time was significantly associated with either the control rate or degree of pain relief. A significant association between the type of facial pain and the pain control rate after GKS was observed (p < 0.001; Pearson chi-square test). In their statistical analysis, the authors accounted for changes in prescription dose over time to prevent the dose rate from being a confounding variable. There was no observable effect of the dose rate or of the treatment duration within the typical period to source replacement.

CONCLUSIONS

Patients with facial pain appear to receive consistent treatment with GKS at any time during the first half-life of the Co sources.
OBJECTIVES
Approximately 8000 patients with trigeminal neuralgia undergo surgery each year in the United States at an estimated cost exceeding $100 million. We compared 3 commonly performed surgeries (microvascular decompression, glycerol rhizotomy, and stereotactic radiosurgery) to evaluate the relative cost-effectiveness of these operations for patients with idiopathic trigeminal neuralgia.

METHODS
Prospective nonrandomized trial at a tertiary referral center from July 1999 to December 2001. One hundred twenty-six consecutive patients underwent 153 operations (microvascular decompression, n=33; glycerol rhizotomy, n=51; stereotactic radiosurgery, n=69). Preoperative characteristics were similar between the groups with respect to sex, pain location, duration of pain, and atypical features. Facial pain outcomes were classified as excellent (no pain, no medications), good (no pain, reduced medications), fair (>50% pain reduction), and poor. The cost per quality adjusted pain-free year was compared between the groups. Mean follow-up was 20.6 months.

RESULTS
Patients having microvascular decompression more commonly achieved and maintained an excellent outcome (85% and 78% at 6 and 24 months) compared with glycerol rhizotomy (61% and 55%, P=0.01) and stereotactic radiosurgery (60% and 52%, P<0.01). No difference was detected between glycerol rhizotomy and stereotactic radiosurgery (P=0.61). The cost per quality adjusted pain-free year was $6,342, $8,174, and $8,269 for glycerol rhizotomy, microvascular decompression, and stereotactic radiosurgery, respectively. Reduction in the average cost of morbidity and additional surgeries to zero did not make either microvascular decompression or stereotactic radiosurgery more cost-effective than glycerol rhizotomy. Both microvascular decompression and stereotactic radiosurgery would be more cost-effective than glycerol rhizotomy if the cost of additional surgeries after glycerol rhizotomy increased 79% and 83%, respectively.

DISCUSSION
This analysis supports the practice of percutaneous surgeries for older patients with medically unresponsive trigeminal neuralgia. At longer follow-up intervals, microvascular decompression is predicted to be the most cost-effective surgery and should be considered the preferred operation for
patients if their risk for general anesthesia is acceptable. More data are needed to assess the role that radiosurgery should play in the management of patients with trigeminal neuralgia.

**J Neurosurg. 2005 Mar;102(3):434-41.**
Gamma knife surgery for trigeminal neuralgia: outcomes and prognostic factors.
Sheehan J, Pan HC, Stroila M, Steiner L.

Lars Leksell Center for Gamma Surgery, Department of Neurological Surgery, University of Virginia Health System, Charlottesville, Virginia 22908, USA. jps2f@virginia.edu

**OBJECT**
Microvascular decompression (MVD) and percutaneous ablation surgery have historically been the treatments of choice for medically refractory trigeminal neuralgia (TN). Gamma knife surgery (GKS) has been used as an alternative, minimally invasive treatment in TN. In the present study, the authors evaluated the long-term results of GKS in the treatment of TN.

**METHODS**
From 1996 to 2003, 151 cases of TN were treated with GKS. In this group, radiosurgery was performed once in 136 patients, twice in 14 patients, and three times in one patient. The types of TN were as follows: 122 patients with typical TN, three with atypical TN, four with multiple sclerosis-associated TN, and seven with TN and a history of a cavernous sinus tumor. In each case, the chosen radiosurgical target was located 2 to 4 mm anterior to the entry of the trigeminal nerve into the pons. The maximal radiation doses ranged from 50 to 90 Gy. The median age of the patients was 68 years (range 22-90 years), and the median time from diagnosis to GKS was 72 months (range 1-276 months). The median follow up was 19 months (range 2-96 months). Clinical outcomes and postradiosurgical magnetic resonance (MR) imaging studies were analyzed. Univariate and multivariate analyses were performed to evaluate factors that correlated with a favorable, pain-free outcome. The mean time to relief of pain was 24 days (range 1-180 days). Forty-seven, 45, and 34% of patients were pain free without medication at the 1-, 2-, and 3-year follow ups, respectively. Ninety, 77, and 70% of patients experienced some improvement in pain at the 1-, 2-, and 3-year follow ups, respectively. Thirty-three (27%) of 122 patients with initial improvement subsequently experienced pain recurrence a median of 12 months (range 2-34 months) post-GKS. Among those whose symptoms recurred, 14 patients underwent additional GKS, six MVD, four glycerol injection, and one patient a percutaneous radiofrequency rhizotomy. Twelve patients (9%) suffered the onset of new facial numbness post-GKS. Changes on MR images post-GKS were noted in nine patients (7%). On univariate analysis, right-sided neuralgia (p = 0.0002) and a previous neurectomy (p = 0.04) correlated with a pain-free outcome; on multivariate analysis, both rightsided neuralgia (p = 0.032) and patient age (p = 0.05) were statistically significant. New onset of facial numbness following GKS correlated with undergoing more than one GKS (p = 0.002).

**CONCLUSIONS**
At the last follow up, GKS effected pain relief in 44% of patients. Some degree of pain improvement at 3 years post-GKS was noted in 70% of patients with TN. Although less effective than MVD, GKS remains a reasonable treatment option for those unwilling or unable to undergo more invasive surgical approaches and offers a low risk of side effects.


Microvascular decompression after gamma knife surgery for trigeminal neuralgia: intraoperative findings and treatment outcomes.

Shetter AG, Zabramski JM, Speiser BL.

Division of Neurological Surgery and Pediatric Oncology, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, Arizona 85013, USA. neuropub@chw.edu

**OBJECT**
The authors sought to determine whether the results of trigeminal microvascular decompression (MVD) are influenced by prior gamma knife surgery (GKS).

**METHODS**
Gamma knife surgery is an established procedure for treating medically intractable trigeminal neuralgia but failures do occur. The authors assessed six patients (two men and four women; mean age 52 years) who experienced pain recurrence after GKS and elected to undergo trigeminal MVD via retrosigmoid craniotomy. Three patients underwent a single GKS to a maximal dose of 80 Gy, whereas three others underwent a second GKS to total of 120 to 135 Gy. At surgery, none of the six patients demonstrated excess arachnoid thickening, grossly apparent changes in the nerve itself, or any other tissue alterations that made successful mobilization of a blood vessel from the trigeminal root entry zone technically more difficult. A single individual had a small atherosclerotic plaque in the superior cerebellar artery near its contact point with the trigeminal nerve. Follow up at a mean of 25.4 months (range 7.5-42 months) indicated that five patients were pain free. One patient had improved but still relied on medications for pain control.

**CONCLUSIONS**
In the authors' experience, trigeminal MVD can be performed without added difficulty in patients who have previously undergone GKS. The success rates seem similar to those normally associated with MVD. Patients who elect the less invasive option of GKS can be assured that trigeminal MVD remains a viable alternative at a later date if further surgery is required.
Gamma knife surgery for trigeminal neuralgia: outcome, imaging, and brainstem correlates.
Cheuk AV, Chin LS, Petit JH, Herman JM, Fang HB, Regine WF.

University of Maryland School of Medicine, Baltimore, MD, USA.

PURPOSE
To review our results with gamma knife surgery (GKS) in the treatment of trigeminal neuralgia (TN),
and to determine whether pain relief, medication usage, and the development of facial numbness are
affected by trigeminal nerve compression, MRI imaging quality, or brainstem radiation dose.

METHODS AND MATERIALS
One hundred twelve patients with TN refractory to medical or surgical management were
treated at the University of Maryland Gamma Knife Center between June 1996 and July 2001. Patients
were treated using a 4-mm shot to the trigeminal nerve, at a point 2-4 mm anterior to the root entry
zone of the nerve into the pons. The median dose prescribed was 75 Gy (range, 60-80 Gy). T1- and T2-
weighted, axial, 1.5-mm-thick MRI images were obtained using three-dimensional gradient echo
acquisition after contrast injection for treatment planning. MRI images were evaluated for imaging
quality (i.e., the adequacy of visualization of the affected prepontine trigeminal nerve), the presence of
trigeminal nerve compression, and the brainstem dose. Follow-up data were obtained via telephone
interviews, and patients were asked to rate their pre-GKS and post-GKS pain using the Barrow
Neurological Institute (BNI) Pain Intensity Scale. Patients were also asked about side effects from GKS
and were asked to rate any facial numbness on the BNI Facial Numbness Scale. Medication use, time to
pain response, and duration of relief were also evaluated.

RESULTS
Ninety-six patients who had follow-up data were included in the analysis. Eighty-six patients
(89.6%) responded to GKS with an improvement in BNI pain class. Ten patients (10.4%) were
found to have an MRI of poor quality, 30 (31.3%) fair quality, and 56 (58.3%) good quality. Forty-two
(43.8%) received 10% of the maximal dose to the brainstem edge, whereas 54 (56.2%) received 20%.
Eleven (11.5%) patients were found to have obvious nerve compression by MRI. Imaging quality (p =
0.1863), presence of compression (p = 0.1147), and brainstem dose (p = 0.3168) did not correlate with
treatment response. There was also no correlation between these variables (MRI quality, compression,
and brainstem dose) and medication use (p = 0.5372, p = 0.0913, p = 0.6832, respectively). Facial
numbness was the only side effect experienced. Thirteen patients reported varying degrees of
facial numbness, but there was no correlation between imaging quality (p = 0.0600),
brainstem dose (p = 0.6773), and presence of compression (p = 0.5785) with the
development of facial numbness.
CONCLUSIONS
Gamma knife surgery is effective in the treatment of TN and has a favorable side effect profile. Treatment response and the development of facial numbness do not correlate with MRI imaging quality, presence of nerve compression, or radiation dose to the brainstem.

Long-term outcome after gamma knife surgery for secondary trigeminal neuralgia.
Régis J, Metellus P, Dufour H, Roche PH, Muracciole X, Pellet W, Grisoli F, Peragut JC.
Department of Stereotactic and Functional Neurosurgery, Timone Hospital, Marseilles, France.

OBJECT
This study was directed to evaluate the potential role of gamma knife surgery (GKS) in the treatment of secondary trigeminal neuralgia (TN). The authors have identified three anatomicoclinical types of secondary TN requiring different radiosurgical approaches.

METHODS
Pain control was retrospectively analyzed in a population of patients harboring tumors of the middle or posterior fossa that involved the trigeminal nerve pathway. This series included 53 patients (39 women and 14 men) treated using GKS between July 1992 and June 1997. The median follow-up period was 55 months. Treatment strategies differed according to lesion type, topography, and size, as well as visibility of the fifth cranial nerve in the prepontine cistern. Three different treatment groups were established. When the primary goal was treatment of the lesion (Group IV, 46 patients) we obtained pain cessation in 79.5% of cases. In some patients in whom GKS was not indicated for treatment of the lesion, TN was treated by targeting the fifth nerve directly in the prepontine cistern if visible (Group II, three patients) or in the part of the lesion including this nerve if the nerve root could not be identified (Group III, four patients). No deaths and no radiosurgically induced adverse effects were observed, but in two cases there was slight hypesthesia (Group IV). The neuropathic component of the facial pain appeared to be poorly sensitive to radiosurgery. At the last follow-up examination, six patients (13.3%) exhibited recurrent pain, which was complete in four cases (8.8%) and partial in two (4.4%).

CONCLUSIONS
The results of GKS regarding facial pain control are very similar to those achieved by microsurgery according to series published in the literature. Nevertheless, the low rate of morbidity and the greater comfort afforded the patient render GKS safer and thus more attractive.
Does increased nerve length within the treatment volume improve trigeminal neuralgia radiosurgery? A prospective double-blind, randomized study.

Flickinger JC, Pollock BE, Kondziolka D, Phuong LK, Foote RL, Stafford SL, Lunsford LD.

Department of Radiation Oncology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.

**PURPOSE**

To test the hypothesis that increasing the nerve length within the treatment volume for trigeminal neuralgia radiosurgery would improve pain relief.

**METHODS AND MATERIALS**

Eighty-seven patients with typical trigeminal neuralgia were randomized to undergo retrogasserian gamma knife radiosurgery (75 Gy maximal dose with 4-mm diameter collimators) using either one (n = 44) or two (n = 43) isocenters. The median follow-up was 26 months (range 1-36).

**RESULTS**

Pain relief was complete in 57 patients (45 without medication and 12 with low-dose medication), partial in 15, and minimal in another 15 patients. The actuarial rate of obtaining complete pain relief (with or without medication) was 67.7% +/- 5.1%. The pain relief was identical for one- and two-isocenter radiosurgery. Pain relapsed in 30 of 72 responding patients. Facial numbness and mild and severe paresthesias developed in 8, 5, and 1 two-isocenter patients vs. 3, 4, and 0 one-isocenter patients, respectively (p = 0.23). Improved pain relief correlated with younger age (p = 0.025) and fewer prior procedures (p = 0.039) and complications (numbness or paresthesias) correlated with the nerve length irradiated (p = 0.018).

**CONCLUSIONS**

Increasing the treatment volume to include a longer nerve length for trigeminal neuralgia radiosurgery does not significantly improve pain relief but may increase complications.
High-dose trigeminal neuralgia radiosurgery associated with increased risk of trigeminal nerve
dysfunction.
Pollock BE, Phuong LK, Foote RL, Stafford SL, Gorman DA.
Department of Neurological Surgery, Mayo Clinic and Foundation, Rochester, Minnesota 55905, USA.
pollock.bruce@mayo.edu

OBJECTIVE
Stereotactic radiosurgery is being used with more frequency in the management of patients with
trigeminal neuralgia. To improve facial pain outcomes, many centers have increased the prescribed
radiation dose to the trigeminal nerve.

METHODS
Between April 1997 and December 1999, 68 patients underwent radiosurgery for trigeminal
neuralgia with use of the Leksell gamma knife (Elekta Instruments, Norcross, GA) and a single 4-
mm isocenter of radiation. Twenty-seven patients (40%) received 70 Gy (low dose) of irradiation
and 41 patients (60%) received 90 Gy (high dose). The groups were similar with regard to age, sex,
duration of pain, number of prior surgeries, and preexisting trigeminal deficits. The primary facial pain
outcomes for analysis were excellent (pain-free, no medications) and good (pain-free, reduced
medications). The mean length of follow-up after radiosurgery was 14.4 months (range, 2-36 mo).

RESULTS
At last follow-up examination, 11 (41%) of the 27 patients with low-dose radiosurgery
remained pain-free compared with 25 (61%) of the 41 patients with high-dose
radiosurgery (P = 0.17). Additional surgery was performed in 12 low-dose patients (44%) and 8 high-
dose patients (20%) (P = 0.05). High-dose radiosurgery was associated with an increased rate of
permanent trigeminal nerve dysfunction (54% versus 15%, P = 0.003). Bothersome dysesthesias
occurred in 13 high-dose patients (32%), whereas only 1 low-dose patient had this
complication (P = 0.01). Three high-dose patients (8%) developed corneal numbness after
radiosurgery. Pain recurred with more frequency in patients not developing trigeminal nerve
dysfunction after radiosurgery (9 of 22 patients, 41 %) compared with those who sustained facial
numbness, paresthesias, or dysesthesias (4 of 27 patients, 15%); however, the difference was not
statistically significant (P = 0.08).

CONCLUSION
Higher doses of radiation may correlate with better facial pain outcomes after radiosurgery for
trigeminal neuralgia. However, the incidence of significant trigeminal nerve dysfunction is markedly
increased after radiosurgery for patients receiving high-dose radiosurgery. Because of the nonselective nature of this ablative technique, dose prescription should be limited to less than 90 Gy.