

1.

**Year:** 2006

**Patient number:** 96

**Author:** Jezková, Jana; Marek, Josef; Hána, Václav; Krsek, Michal; Weiss, Vladimír; Vladyka, Vilibald; Lisák, Roman; Vymazal, Josef; Pecen, Ladislav

**Reference:** Clinical endocrinology, 64, 5, 588-95, 2006

**Title:** Gamma knife radiosurgery for acromegaly--long-term experience

**Abstract:** **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 mm<sup>3</sup> (median 1350 mm<sup>3</sup>). **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.

2.

**Year:** 2006

**Patient number:** 312

**Author:** Jia, Q.; Xu, D. S.; Lin, Y. G.; Zhang, Z. Y.; Li, Y. H.; Zhang, Y. P.; Liu, D.; Liu, X. M.; Zheng, L. G.

**Reference:** Chinese Journal of Contemporary Neurology and Neurosurgery, 6, 4, 283-287, 2006

**Title:** Gamma knife for pituitary adenomas treatment

**Abstract:** **Objective:** To evaluate curative effect, plasma hormone level and main complications after gamma knife radiosurgery (GKRS) in patients with pituitary adenomas. **Methods:** Among 417 patients with pituitary adenomas undergoing GKRS procedures in our medical center from September 1995 to December 2004, 312 patients achieved complete follow-up including 78 non-functional pituitary adenomas and 234 functional pituitary adenomas (124 prolactinomas, 37 growth hormone- secreting adenomas, 12 adrenocorticotrophic hormone-secreting adenomas, 1 thyroid-stimulating

hormone-secreting adenomas, 8 follicle-stimulating hormone adenomas, and 52 mixed adenomas). Of 312 patients followed up (117 male, 195 female), 139 were treated for recurrent or residual adenomas after surgery or radiotherapy. The mean follow-up period was 30.50 months. The clinical symptom, tumor diameter and endocrinal function were analyzed retrospectively. Results: In this series, complete tumor disappearance was observed in 25 cases (8.01%), regression in 152 cases (48.72%), stability in 129 cases (41.35%) and enlarged tumor in 6 cases (1.92%). The total tumor control rate was 98.08% (306/312). Of the patients with functional pituitary adenomas, plasma hormone level was normalized in 77 patients (32.91%), decreased in 102 patients (43.59%) and without significant changes in 55 patients (23.50%) compared to the hormone level before GKRS. GKRS was tolerated well in most cases. Acute toxicity was uncommon, but late adverse effect was noted in 5 patients with decreased visual acuity and in 8 patients with hypopituitarism. Conclusion: GKRS is a safe and effective therapy in selected patients with pituitary adenomas.

3.

**Year:** 2006

**Patient number:** 51

**Author:** Ma, Zhi ming; Qiu, Bin; Hou, Yong hong; Liu, Yun sheng

**Reference:** Zhong nan da xue xue bao. Yi xue ban = Journal of Central South University. Medical sciences, 31, 5, 714-6, 2006

**Title:** Gamma knife treatment for pituitary prolactinomas

**Abstract:** OBJECTIVE: To evaluate the outcome of gamma knife for prolactinomas.

METHODS: Eighty-nine patients were treated by gamma knife and 51 were followed up. The dose to the tumor margin ranged from 18 Gy to 35 Gy (mean 26.1 Gy). The maximum radiation dose varied from 36 Gy to 60 Gy (mean 50.41 Gy). The mean tumor diameter was 15.5 mm (5 - 26 mm). RESULTS: The follow-up data were available for 51 patients ranging from 6 to 108 months (mean 37 months). The tumor growth control rate was 100%. The endocrinological remission rate was 40%. The rate of hypopituitarism was 17.6%. CONCLUSION: Gamma knife radiosurgery can be used as a primary treatment for selected prolactinomas, especially for pituitary microadenomas.

4.

**Year:** 2006

**Patient number:** 100

**Author:** Mingione, Vincenzo; Yen, Chun Po; Vance, Mary Lee; Steiner, Melita; Sheehan, Jason; Laws, Edward R.; Steiner, Ladislau

**Reference:** Journal of neurosurgery, 104, 6, 876-83, 2006

**Title:** Gamma surgery in the treatment of nonsecretory pituitary macroadenoma

**Abstract:** 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.

5.

**Year:** 2006

**Patient number:** 23

**Author:** Pouratian, Nader; Sheehan, Jason; Jagannathan, Jay; Laws, Edward R., Jr.; Steiner, Ladislau; Vance, Mary L.

**Reference:** Neurosurgery (Hagerstown), 59, 2, 255-264, 2006

**Title:** Gammaknife radiosurgery for medically and surgically refractory prolactinomas

**Abstract:** **OBJECTIVE:** Experience with gamma knife radiosurgery (GKRS) for prolactinomas is limited because of the efficacy of medical and surgical intervention. Patients who are refractory to medical and/or surgical therapy may be treated with GKRS. We characterize the efficacy of GKRS for medically and Surgically refractory prolactinomas .**METHODS:** We reviewed our series of patients with prolactinomas who were treated with GKRS after failing medical and surgical intervention who had at least 1 year of follow-up.**RESULTS:** Twenty-three patients were included in analysis of endocrine outcomes (median and average follow-up of 55 and 58 mo, respectively) and 28 patients were included in analysis of imaging outcomes (median and average follow-up of 48 and 52 mo, respectively). Twenty-six percent of patients achieved a normal serum prolactin (remission) with an average time of 24.5 months. Remission was significantly associated with being off of a dopamine agonist at the time of GKRS and a tumor volume less than 3.0 cm<sup>3</sup> (P < 0.05 for both). Long-term image-based volumetric control was achieved in 89% of patients. Complications included new pituitary hormone deficiencies in 28% of patients and cranial nerve palsy in two patients (7%).**CONCLUSION:** Clinical remission in

26% of treated patients is a modest result. However, because the GKRS treated tumors were refractory to other therapies and because complication rates were low, GKRS should be part of the armamentarium for treating refractory prolactinomas. Patients with tumors smaller than 3.0 cm(3) and who are not receiving dopamine agonist at the time of treatment will likely benefit most.

6.

**Year:** 2006

**Patient number:** literature review

**Author:** Sheehan, Jason P.; Jagannathan, Jay; Pouratian, Nader; Steiner, Ladislau

**Reference:** Frontiers of hormone research, 34, 185-205, 2006

**Title:** Stereotactic radiosurgery for pituitary adenomas: a review of the literature and our experience

**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.

7.

**Year:** 2006

**Patient number:** 17

**Author:** Tang, B. N. T.; Levivier, M.; Heureux, M.; Wikler, D.; Massager, N.; Devriendt, D.; David, P.; Dumarey, N.; Corvilain, B.; Goldman, S.

**Reference:** European journal of nuclear medicine and molecular imaging, 33, 2, 169-78, 2006

**Title:** 11C-methionine PET for the diagnosis and management of recurrent pituitary adenomas

**Abstract:** **PURPOSE:** The detection of recurrent pituitary adenoma by magnetic resonance imaging (MRI) is rendered uncertain by the tissue remodelling that follows surgery or radiotherapy. We aimed to evaluate the contribution of PET with 11C-methionine (MET-PET) in the detection and management of recurrent pituitary adenoma. **METHODS:** Thirty-three patients with pituitary adenoma were evaluated postoperatively by MET- PET, either because of biological evidence of active residual tumour or because of MRI demonstration of non-functional adenoma growth. We studied 24 secreting adenomas and nine non-functional adenomas. **RESULTS:** In 30 patients,

MET-PET detected abnormally hypermetabolic tissue. In 14 out of these, MRI did not differentiate between residual tumour and scar formation. In nine of these 14 cases, major therapeutic decisions were undertaken (radiosurgery and surgery). In another group of 16 patients, both MET-PET and MRI detected abnormal tissue. In one case, neither MRI nor MET-PET detected adenomatous tissue. Finally, abnormal tissue was detected in two patients on MRI solely. In these two cases, failure of MET-PET to reveal the adenoma was attributable to concomitant inhibitory therapy. The sensitivity of MET-PET and MRI varied as a function of the tumour type: all non-functional adenomas were localised by both modalities, while MET-PET detected all adrenocorticotrophic hormone-secreting adenomas whereas MRI depicted only one of these eight lesions. Fifteen out of 17 patients treated by radiosurgery showed clinical improvement after treatment. CONCLUSION: We suggest that MET-PET is a sensitive technique complementary to MRI for the detection of residual or recurrent pituitary adenomas. It should gain a place in the efficient management of these tumours.

8.

**Year:** 2006

**Patient number:** 120

**Author:** Yuan, Yu hui; Dong, Xin ming; Yu, Hong wei; Guan, Jun hong; Wang, Cheng lin

**Reference:** Zhonghua wai ke za zhi (Chinese journal of surgery), 44, 6, 416-9, 2006

**Title:** Gamma knife for hypersecreting pituitary adenom: analysis of 120 cases

**Abstract:**OBJECTIVE: To estimate the efficacy of Gamma knife radiosurgery (GKR) especially as a primary surgical treatment for hypersecreting pituitary adenoma.

METHODS: One hundred and twenty cases with hypersecreting pituitary adenoma had been treated by Gamma knife radiosurgery. The clinical date had been analysed retrospectively. The tumor margin was covered by an isodose ranging from 45% to 70%. The margin dose was 15 to 32 Gy (mean 28.5 Gy) and the maximum dose varied from 35 to 70 Gy (mean 45.5 Gy). The total number of isocenter was 165 (mean 1-3). RESULTS: One hundred and eleven cases had been followed-up by hormone level, and 104 cases had been followed-up by image of MRI. The mean follow-up duration was 12-72 months (mean 36 months). The control rate of hormone level was 48.6%, the control rate of tumor growth was 96.2%, the incidence of hypopituitarism was in 2.7% and the incidence of tumor apoplexy was in 0.9% in followed-up cases. CONCLUSIONS: As a primary surgical treatment for hypersecreting pituitary adenoma, GKR can be effective and safe in controlling tumor growth and inducing hormonal normalization.

9.

**Year:** 2005

**Patient number:** 82

**Author:** Castinetti, Frédéric; Taieb, David; Kuhn, Jean Marc; Chanson, Philippe; Tamura, Manabu; Jaquet, Philippe; Conte, Devolx Bernard; Régis, Jean; Dufour, Henry; Brue, Thierry

**Reference:**The Journal of clinical endocrinology and metabolism, {J-Clin-

Endocrinol-Metab}, Aug 2005 (epub: 17 May 2005), vol. 90, no. 8, p. 4483-8, ISSN: 0021-972X.

**Title:** Outcome of gamma knife radiosurgery in 82 patients with acromegaly: correlation with initial hypersecretion

**Abstract:** 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.

10.

**Year:** 2005

**Patient number:** 44

**Author:** Gutt, B.; Wowra, B.; Alexandrov, R.; Uhl, E.; Schaaf, L.; Stalla, G. K.; Schopohl, J.

**Reference:** Experimental and clinical endocrinology & diabetes, 113, 4, 219-24, 2005

**Title:** Gamma-knife surgery is effective in normalising plasma insulin-like growth factor I in patients with acromegaly

**Abstract:** OBJECTIVE: For patients in whom acromegaly persists despite pituitary surgery or drug treatment, gamma-knife surgery represents an additional treatment option. Considering carefully the different reported biochemical outcomes, the central point is whether gamma-knife radiosurgery has advantages compared to conventional radiotherapy or, furthermore, to newer medical therapies, such as long-acting somatostatin analogues or growth hormone receptor antagonists. DESIGN AND METHODS: We report the outcome of 44 patients with acromegaly, who received gamma-knife surgery with the Leksell gamma knife. The median follow-up time was 1.9 years (0.5-4.3 years) post-radiosurgery. 43 of 44 patients had previously undergone pituitary surgery. RESULTS: Immediately prior to gamma-knife surgery, median xULN of

patients' serum IGF-I was 1.9 times above upper limit of normal (range: 0.5-8.9 xULN (multiple of upper limit of normal range)). There was a significant decline of serum IGF-I at patients' final follow-up. We found a normal age-adjusted IGF-I in 21/44 patients (xULN of IGF-I<1). Furthermore, as the number of treated patients increased, we found an improvement in remission rate, which let us assume that there was a learning effect for the gamma-knife performing team over time. In addition, the median adenoma size decreased from 1.5 ml (0.1-6.9 ml) prior to gamma-knife therapy to 0.3 ml (no rest vol. detectable-2.4 ml) at patients' last visit. CONCLUSION: We have shown that pituitary gamma-knife surgery is effective in lowering serum IGF-I levels. At the end of the follow-up period, 48 % of our cohort had normal age-adjusted IGF-I levels.

11.

**Year:** 2005

**Patient number:** 17

**Author:** Hayashi, Motohiro; Taira, Takaomi; Ochiai, Taku; Chernov, Mikhail; Takasu, Yuichi; Izawa, Masahiro; Kouyama, Nobuo; Tomida, Mihoko; Tokumaru, Osamu; Katayama, Yoko; Kawakami, Yoriko; Hori, Tomokatsu; Takakura, Kintomo

**Reference:** Journal of neurosurgery, 102, 38-41, 2005

**Title:** Gamma knife surgery of the pituitary: new treatment for thalamic pain syndrome

**Abstract:**OBJECT: Although reports in the literature indicate that thalamic pain syndrome can be controlled with chemical hypophysectomy, this procedure is associated with transient diabetes insipidus. It was considered reasonable to attempt gamma knife surgery (GKS) to the pituitary gland to control thalamic pain. METHODS: Inclusion criteria in this study were poststroke thalamic pain, failure of all other treatments, intolerance to general anesthetic, and the main complaint of pain and not numbness. Seventeen patients met these criteria and were treated with GKS to the pituitary. The target was the pituitary gland together with the border between the pituitary stalk and the gland. The maximum dose was 140 to 180 Gy. All patients were followed for more than 3 months. CONCLUSIONS: An initial significant pain reduction was observed in 13 (76.5%) of 17 patients. Some patients experienced pain reduction within 48 hours of treatment. Persistent pain relief for more than 1 year was observed in five (38.5%) of 13 patients. Rapid recurrence of pain in fewer than 3 months was observed in four (30.8%) of 13 patients. The only complication was transient diabetes insipidus in one patient. It would seem that GKS of the pituitary might have a role to play in thalamic pain arising after a stroke.

12.

**Year:** 2005

**Patient number:** 31

**Author:** Iwai, Yoshiyasu; Yamanaka, Kazuhiro; Yoshioka, Katsunobu

**Reference:** Neurosurgery, 56, 4, 699-705, 2005

**Title:** Radiosurgery for nonfunctioning pituitary adenomas

**Abstract:**OBJECTIVE: We evaluated the effectiveness of gamma knife radiosurgery in the treatment of nonfunctioning pituitary adenomas. METHODS: Between January 1994 and December 1999, we treated 34 patients with nonfunctioning pituitary adenomas. Thirty-one of these patients were followed for more than 30 months. Their mean age was 52.9 years. All patients underwent resection before radiosurgery. In four patients, treatment was performed with staged radiosurgery. The treatment volume was 0.7 to 36.2 cm<sup>3</sup> (median, 2.5 cm<sup>3</sup>). The treatment dose ranged from 8 to 20 Gy (median, 14.0 Gy) to the tumor margin. In 15 patients (48.4%), the tumor either compressed or was attached to the optic apparatus. The maximum dose to the optic apparatus was from 2 to 11 Gy (median, 8 Gy). RESULTS: Patients were followed for 30 to 108 months (median, 59.8 mo). The tumor size decreased in 18 patients (58.1%), remained unchanged in 9 patients (29.0%), and increased in four patients (12.9%). The 5-year actual tumor growth control rate was 93%. Among patients with tumor growth, two cases were secondary to cyst formation. Two patients (6.5%) required adrenal and thyroid hormonal replacement during the follow-up period after radiosurgery because of radiation-induced endocrinopathy. None of the patients sustained new cranial nerve deficits, which included optic neuropathy. CONCLUSION: In this series, radiosurgery had a high tumor growth control rate during the long-term follow-up period. Furthermore, we observed a low morbidity rate, with endocrinopathies and optic neuropathies. This low rate included even patients in whom the tumor compressed or was attached to the optic apparatus. We emphasize the necessity of long-term follow-up to evaluate late complications.

13.

**Year:** 2005

**Patient number:** 28

**Author:** Iwai, Yoshiyasu; Yamanaka, Kazuhiro; Yoshioka, Kastunobu; Yoshimura, Masaki; Honda, Yuji; Matsusaka, Yasuhiro; Komiyama, Masaki; Yasui, Toshihiro

**Reference:** No shinkei geka. Neurological surgery, 33, 8, 777-83, 2005

**Title:** The usefulness of adjuvant therapy using gamma knife radiosurgery for the recurrent or residual nonfunctioning pituitary adenomas

**Abstract:**We evaluated the treatment results of nonfunctioning pituitary adenomas in the era of radiosurgery. Between January 1994 and December 2003, we operated on 44 patients with nonfunctioning pituitary adenomas. 43 patients were operated on by transsphenoidal surgery and one patient was operated on by the transcranial approach. Total removal was able to be achieved in 13 patients (30%). Gamma knife radiosurgery was performed for residual tumor in 26 patients and for recurrence in 2 patients. The mean tumor diameter at the gamma knife radiosurgery was 18.2 mm (7.9 to 26.3 mm). The treatment dose was a mean of 12.3 Gy (8 to 16 Gy) to the tumor margin. The mean follow-up period after radiosurgery was 36.4 months. Tumor growth control was able to be achieved in 26 patients (93%). Two patients (7%) required adrenal and thyroid hormonal replacement during the follow-up period after radiosurgery due to radiation-induced endocrinopathy. None of the patients suffered from new cranial nerve deficits. This included optic neuropathy. Surgical resection using transsphenoidal surgery and subsequent gamma knife radiosurgery for residual and recurrent tumor proved to have a

highly effective tumor growth control rate, and maintained the quality of life in patients with nonfunctioning pituitary adenomas.

14.

**Year:** 2005

**Patient number:** 67

**Author:** Kobayashi, Tatsuya; Mori, Yoshimasa; Uchiyama, Yukio; Kida, Yoshihsa; Fujitani, Shigeru

**Reference:** Journal of neurosurgery, 102, 119-23, 2005

**Title:** Long-term results of gamma knife surgery for growth hormone-producing pituitary adenoma: is the disease difficult to cure?

**Abstract:**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 cm<sup>3</sup>. 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.

15.

**Year:** 2005

**Patient number:** 51

**Author:** Picozzi, Piero; Losa, Marco; Mortini, Pietro; Valle, Micol Angela; Franzin, Alberto; Attuati, Luca; Ferrari, da Passano Camillo; Giovanelli, Massimo

**Reference:** Journal of neurosurgery, 102, 71-4, 2005

**Title:** Radiosurgery and the prevention of regrowth of incompletely removed nonfunctioning pituitary adenomas

**Abstract:**OBJECT: The authors studied the efficacy of gamma knife radiosurgery (GKS) in the prevention of regrowth of nonfunctioning pituitary adenomas (NPA). METHODS: One hundred nineteen patients were included in this study and were divided into two groups. All patients had undergone surgery in our department and recurrent or residual adenoma was demonstrated on postoperative MR imaging. Group A consisted of 68

patients who were followed without additional treatment. Group B was composed of 51 patients who received GKS within 1 year after microsurgery. There was no significant demographic difference between the two groups. In Group B the mean margin dose was 16.5 +/- 0.3 Gy (range 13-21 Gy). Fifty one and one tenth percent of patients in Group A were recurrence free at 5 years and 89.8% in Group B ( $p < 0.001$ ). In Group B patients, tumor volume decreased from a baseline value of 2.4 +/- 0.2 cm<sup>3</sup> to 1.6 +/- 0.2 cm<sup>3</sup> at last follow up ( $p < 0.001$ ). **CONCLUSIONS:** The results of this study suggest that GKS is effective in controlling growth of residual NPA for at least 5 years following initial maximal surgical debulking compared with no radiation therapy. Thus, GKS is recommended after microsurgery when visible tumor can be detected on imaging studies.

16.

**Year:** 2005

**Patient number:** Review of literature

**Author:** Sheehan, Jason P.; Niranjan, Ajay; Sheehan, Jonas M.; Jane, John A., Jr.; Laws, Edward R.; Kondziolka, Douglas; Flickinger, John; Landolt, Alex M.; Loeffler, Jay S.; Lunsford, L. Dade

**Reference:** Journal of neurosurgery, 102, 4, 678-91, 2005

**Title:** Stereotactic radiosurgery for pituitary adenomas: an intermediate review of its safety, efficacy, and role in the neurosurgical treatment armamentarium

**Abstract:**OBJECT: Pituitary adenomas are very common neoplasms, constituting between 10 and 20% of all primary brain tumors. Historically, the treatment armamentarium for pituitary adenomas has included medical management, microsurgery, and fractionated radiotherapy. More recently, radiosurgery has emerged as a viable treatment option. The goal of this research was to define more fully the efficacy, safety, and role of radiosurgery in the treatment of pituitary adenomas. **METHODS:** Medical literature databases were searched for articles pertaining to pituitary adenomas and stereotactic radiosurgery. Each study was examined to determine the number of patients, radiosurgical parameters (for example, maximal dose and tumor margin dose), duration of follow-up review, tumor growth control rate, complications, and rate of hormone normalization in the case of functioning adenomas. A total of 35 peer-reviewed studies involving 1621 patients were examined. Radiosurgery resulted in the control of tumor size in approximately 90% of treated patients. The reported rates of hormone normalization for functioning adenomas varied substantially. This was due in part to widespread differences in endocrinological criteria used for the postradiosurgical assessment. The risks of hypopituitarism, radiation-induced neoplasia, and cerebral vasculopathy associated with radiosurgery appeared lower than those for fractionated radiation therapy. Nevertheless, further observation will be required to understand the true probabilities. The incidence of other serious complications following radiosurgery was quite low. **CONCLUSIONS:** Although microsurgery remains the primary treatment modality in most cases, stereotactic radiosurgery offers both safe and effective treatment for recurrent or residual pituitary adenomas. In rare instances, radiosurgery may be the best initial treatment for patients with pituitary adenomas. Further refinements in the radiosurgical technique will likely lead to improved outcomes.

17.

**Year:** 2004

**Patient number:** 76

**Author:** Kuo, John S.; Chen, Joseph C. T.; Yu, Cheng; Zelman, Vladimir; Giannotta, Steven L.; Petrovich, Zbigniew; MacPherson, Dana; Apuzzo, Michael L. J.

**Reference:** Neurosurgery, 54, 6, 1385-93, 2004

**Title:** Gamma knife radiosurgery for benign cavernous sinus tumors: quantitative analysis of treatment outcomes

**Abstract:**OBJECTIVE: We review our 8-year experience with gamma knife radiosurgery (GKRS) for the treatment of patients with benign cavernous sinus tumors and present a quantitative analysis of factors relevant to treatment outcomes. METHODS: From 1994 to 2002, a total of 139 patients with benign cavernous sinus tumors were treated in 145 sessions. Their median age was 53 years, and the median follow-up was 3.5 years. The tumors included 57 meningiomas, 76 pituitary tumors (49 nonfunctional adenomas, 15 prolactinomas, 5 adrenocorticotrophic hormone-secreting tumors, 6 growth hormone-secreting tumors, and 1 plurihormone-secreting tumor), 4 schwannomas, 1 hemangioma, and 1 paraganglioma. Sekhar tumor grades were as follows: I, n = 28 (20%); II, n = 42 (30%); III, n = 42 (30%); IV, n = 19 (14%); and V, n = 8 (6%). The median tumor volume was 3.4 cm<sup>3</sup>, and the median prescribed dose was 15 Gy defined to the 50% isodose line. RESULTS: A total of 136 treated tumors (97.8%) were well controlled by GKRS, with low morbidity. For meningiomas, 29 tumors (51%) were unchanged and 26 (46%) were smaller at a median of 15.2 months. For pituitary tumors, 50 (66%) were unchanged and 25 (33%) were smaller at a median of 20.6 months. Improvement in cranial nerve (CN) function was seen in 19 (36.5%) of 52 patients with pre-GKRS deficits, and 3 patients (2.2%) developed new stable CN deficits after GKRS: 1 patient developed IVth

18.

**Year:** 2004

**Patient number:** 77

**Author:** Kuo, John S.; Yu, Cheng; Giannotta, Steven L.; Petrovich, Zbigniew; Apuzzo, Michael L. J.

**Reference:** Neurosurgery, 55, 1, 168-72, 2004

**Title:** The Leksell gamma knife Model U versus Model C: a quantitative comparison of radiosurgical treatment parameters

**Abstract:**OBJECTIVE: We present a quantitative comparison of radiosurgery treatments for cavernous sinus tumors using the Leksell gamma knife Model U versus the Model C with automatic positioning system (APS) (Elekta Instruments, Norcross, GA). METHODS: At our medical center from August 1994 through May 2000, the Model U was used to treat 96 patients (37 men (39%) and 59 women (61%); median age, 54.5 yr) with benign cavernous sinus tumors: 43 meningiomas (45%), 48 pituitary tumors (50%), and 5 others

(5%). From June 2000 through April 2002, the Model C with APS treated 45 patients (20 men (44%) and 25 women (56%); median age, 51.4 yr) with 15 meningiomas (33%), 29 pituitary tumors (65%), and 1 schwannoma (2%). The two groups had similar treated tumor volumes (Model U mean, 4.3 cm<sup>3</sup>; Model C mean, 4.2 cm<sup>3</sup>), equivalent tumor distances from critical structures (optic nerve, chiasm, and pons), comparable distributions in Sekhar tumor grades, and the same median prescribed dose of 15 Gy to the 50% isodose line at the tumor periphery. All planning and treatments were performed by the same radiosurgery team to minimize dosage to adjacent critical tissues and to optimize conformity index. RESULTS: Analysis of multiple treatment parameters showed that the Model C plans were superior. Model C treatments had an improved conformity index (Model U mean, 1.7; Model C mean, 1.6; P < 0.02) and a lower underdosed tumor volume (Model U mean, 0.4 cm<sup>3</sup>; Model C mean, 0.1 cm<sup>3</sup>; P < 0.004). The total treated volume and the excess treated volume were similar. The Model C group had a reduction in optic chiasm dose (Model C mean dose, 3.8 Gy; Model U mean dose, 5.3 Gy; P < 0.0001). The average number of isocenters was slightly higher for the Model C group (6.7 versus 6 for the Model U), but with a lower mean number of collimator sizes (1 versus 2 for the Model U). Model C plans required a mean of 93 fewer plugs per treatment, thus contributing to an estimated 67.6 minutes saved per treatment session. CONCLUSION: Comparison of radiosurgery treatments using the Leksell gamma knife Model U versus the Model C with APS was performed by quantitative analysis of treatment parameters on a cohort of benign cavernous sinus tumors. Treatment plans using the Model C resulted in better tumor coverage (improved conformity, less underdosed tumor volume) and decreased optic chiasm dose. An estimated average of 1 hour was saved per treatment when using the Model C with APS.

19.

**Year:** 2004

**Patient number:** Review of literature

**Author:** Laws, Edward R.; Sheehan, Jason P.; Sheehan, Jonas M.; Jagnathan, Jay; Jane, John A., Jr.; Oskouian, Rod

**Reference:** Journal of neuro-oncology, 69, 1-3, 257-72, 2004

**Title:** Stereotactic radiosurgery for pituitary adenomas: a review of the literature

**Abstract:** OBJECTIVE: Pituitary adenomas are very common neoplasms and represent between 10 and 20% of all primary brain tumors. Historically, the treatment armamentarium for pituitary adenomas included medical management, microsurgery, and fractionated radiotherapy. More recently, radiosurgery has emerged as a viable treatment option. The goal of this research is to define accurately the efficacy, safety, and role of radiosurgery for treatment of pituitary adenomas. METHODS: Medical literature databases from 1965 to 2003 were searched for articles pertaining to pituitary adenomas and stereotactic radiosurgery. Each study was evaluated for the number of patients, radiosurgical parameters (e.g. tumor margin dose), length of follow-up, tumor growth control rate, complications, and rate of hormonal normalization in the case of functioning adenomas. RESULTS: A total of 34 published studies including 1567 patients were reviewed. Radiosurgery offers a tumor growth control rate of approximately 90%. The

reported rates of hormonal normalization for functioning adenomas vary substantially. This range is in part due to widespread differences in endocrinological criteria utilized for post- radiosurgical assessment. Thus far, the risks of radiation induced neoplasia and cerebral vasculopathy associated with radiosurgery appear to be lower than for fractionated radiation therapy. The incidence of other serious complications following radiosurgery is quite low. **CONCLUSIONS:** Although surgical resection typically is the primary treatment modality, stereotactic radiosurgery offers safe and effective treatment for recurrent or residual pituitary adenomas. In rare instances, radiosurgery may be the best initial treatment for patients with pituitary adenomas. Refinements in the radiosurgical technique will likely lead to improved outcomes.

20.

**Year:** 2004

**Patient number:** 10

**Author:** Levivier, Marc; Massager, Nicolas; Wikler, David; Lorenzoni, José; Ruiz, Salvador; Devriendt, Daniel; David, Philippe; Desmedt, Françoise; Simon, Stéphane; Van, Houtte Paul; Brotchi, Jacques; Goldman, Serge

**Reference:** Journal of nuclear medicine, 45, 7, 1146-54, 2004

**Title:** Use of stereotactic PET images in dosimetry planning of radiosurgery for brain tumors: clinical experience and proposed classification

**Abstract:** We developed a technique that allows the routine integration of PET in stereotactic neurosurgery, including radiosurgery. We report our clinical experience with the combined use of metabolic (i.e., PET) and anatomic (i.e., MRI and CT) images for the radiosurgical treatment of brain tumors. We propose a classification describing the relative role of the information provided by PET in this multimodality image-guided approach. **METHODS:** Between December 1999 and March 2003, 57 patients had stereotactic PET as part of their image acquisition for the planning of gamma knife radiosurgery. Together with stereotactic MRI and CT, stereotactic PET images were acquired on the same day using either (18)F-FDG or (11)C-methionine. PET images were imported in the planning software for the radiosurgery dosimetry, and the target volume was defined using the combined information of PET and MRI or CT. To analyze the specific contribution of the PET findings, we propose a classification that reflects the strategy used to define the target volume. **RESULTS:** The patients were offered radiosurgery with PET guidance when their tumor was ill-defined and we anticipated some limitation of target definition on MRI alone. This represents 10% of the radiosurgery procedures performed in our center during the same period of time. There were 40 primary brain lesions, 7 metastases, and 10 pituitary adenomas. Abnormal PET uptake was found in 62 of 72 targets (86%), and this information altered significantly the MRI-defined tumor in 43 targets (69%). **CONCLUSION:** The integration of PET in radiosurgery provides additional information that opens new perspectives for the optimization of the treatment of brain tumors.

21.

**Year:** 2004

**Patient number:** 305

**Author:** Liscák, R.; Vladyka, V.; Marek, J.

**Reference:** Prakticky Lekar, 84, 3, 133-139, 2004

**Title:** Application of radiosurgery in the treatment of pituitary adenoma

**Abstract:** The goal of pituitary adenoma radiosurgery is to halt tumor growth, to normalize hormonal hypersecretion if present, and to maintain the performance of a normal hypophysis and functionally important structures around the sella, namely the optic nerve. The minimum distance required between the irradiated target and the optic pathway should be reassessed. For Gamma knife model B (or C) the limit should be 2 mm for secreting adenomas and, in the case of non-secreting adenomas, direct contact of the adenoma with the optic chiasm may be tolerated where only a short segment is affected of the visual pathway. During the midterm of the follow up period, an anti-proliferative effect was achieved in all 305 evaluated patients and 70% of adenomas decreased in size usually within 2 years following radiosurgery. Hormonal normalisation of hypersecreting adenomas is comparable with the results of transsphenoidal microsurgery, apart from the latency, which is usually 2 years. During this period hypersecretion was arrested in 38% of patients with acromegaly, in 90% with Cushing's disease and in 54% with prolactinoma. The most important factor influencing post-irradiation hypopituitarism seems to be the mean dose applied to the hypophysis. The current position of radiosurgery in the majority of cases is as an adjuvant treatment for residual or recurrent adenomas after previous microsurgery. In selected cases radiosurgery may be used as a primary treatment, e.g. in patients with contraindications of overall anaesthesia in patients, where the treatment effect is not urgent in the patients who refuse to undergo open surgery.

22.

**Year:** 2004

**Patient number:** 54

**Author:** Losa, Marco; Valle, Micol; Mortini, Pietro; Franzin, Alberto; da, Passano Camillo Ferrari; Cenzato, Marco; Bianchi, Stefania; Picozzi, Piero; Giovanelli, Massimo

**Reference:** Journal of neurosurgery, 100, 3, 438-44, 2004

**Title:** Gamma knife surgery for treatment of residual nonfunctioning pituitary adenomas after surgical debulking

**Abstract:** OBJECT: Radiation therapy diminishes the risk of recurrence of incompletely removed nonfunctioning pituitary adenoma (NPA). The authors evaluated the efficacy and safety of gamma knife surgery (GKS) in patients with residual NPA following surgical debulking of the tumor. METHODS: Fifty-four patients, 26 men and 28 women, ranging in age from 29 to 72 years underwent gamma knife treatment. Baseline and follow-up studies involved magnetic resonance imaging, hormone evaluation, and neuroophthalmological examination 6 and 12 months after GKS and at yearly intervals thereafter. The mean follow up after GKS was 41.1 +/- 3.1 months. Two of 52 patients undergoing follow up had a recurrence 40 and 49 months after GKS. In both of these patients the treated lesion had reduced in size, but a new lesion appeared in the

contralateral side of the sella turcica. The recurrence-free interval at 5 years was 88.2% (95% confidence interval 72.6-100%). Tumor volume decreased from a baseline value of 2.3 +/- 0.2 to 1.7 +/- 0.2 cm<sup>3</sup> at the last follow up (p < 0.001). Twenty-two patients (42.3%) had a 20% or greater reduction in tumor volume. The administered radiation dose had been significantly higher in patients who experienced tumor reduction. Visual function and motility did not deteriorate in any patient. New cases of hypogonadism, hypothyroidism, and hypoadrenalism occurred in 12.5, 8.6, and 2.3%, respectively, of assessable patients at risk. **CONCLUSIONS:** Gamma knife surgery was effective in controlling the growth of residual NPA after previously performed maximal surgical debulking. The major advantage of GKS compared with fractionated radiotherapy seems to be a lower risk of side effects, especially a lower risk of hypopituitarism.

23.

**Year:** 2004

**Patient number:** 60

**Author:** Muacevic, A.; Uhl, E.; Wowra, B.

**Reference:** Acta neurochirurgica. Supplement, 91, 51-4, 2004

**Title:** Gamma knife radiosurgery for nonfunctioning pituitary adenomas

**Abstract:** The efficacy of gamma knife radiosurgery (GKS) for non-functioning pituitary adenomas (NPAs) has been assessed. Sixty patients with NPA were treated by GKS. Complete neurological and endocrinological follow-up information was available for 51 patients. Follow-up examinations included stereotactic magnetic resonance imaging for sequential measurements of the NPA volume. The median dose to the tumor margin was 16.5 Gy (range 11-20 Gy). The mean prescription isodose was 50% (range 45-75%). All patients underwent surgery for NPA before GKS. Fractionated radiotherapy was not applied. Median follow up after GKS was 21,7 months. Actuarial recurrence-free survival was 95% after three years with respect to a single GKS and 100% for patients who underwent repeated GKS. No neurological side effects were detected. Two patients developed new partial pituitary insufficiency after radiosurgery. Postoperative GKS for residual or recurrent small fragments of NPAs is an effective and safe treatment option. The follow-up examination for NPAs should include tumor volumetric analysis.

24.

**Year:** 2004

**Patient number:** 116

**Author:** Qiu, Bin; Ma, Zhi Ming; Liu, Yun Sheng; Hou, Yong Hong; Tang, Jian Bing

**Reference:** Zhong nan da xue xue bao. Yi xue ban = Journal of Central South University. Medical sciences, 29, 4, 463-6, 2004

**Title:** Gamma knife treatment for pituitary adenomas

**Abstract:** **OBJECTIVE:** To evaluate the function and effect of Gamma knife radiosurgery (GKR) in controlling the tumor growth and improving endocrinological abnormality of pituitary adenomas. **METHODS:** Two hundred and twenty-eight cases of pituitary

adenoma were treated with Leksell Gamma knife. 1.0 Tesla MRI and Gamma-Plan system were used to orientate the tumor. The margin dose was 12 - 35 Gy, mean 21.3 Gy; the center dose was 24 - 70 Gy, mean 46.6 Gy (NFA, 31.8 Gy; FA, 50.3 Gy). RESULTS: One hundred and sixteen cases (NFA, 28; FA, 88) were followed up for 4 - 67 months, and the mean was 27.4 months. The growth of tumors in 113 cases (97.4%) was controlled. The tumor volume became smaller in 98 cases (84.5%). Three cases (2.6%) grew larger in tumor size. A significant decrease of excessive hormone production was seen in 89.8% of the patients, and the endocrinological normalization rate was 49.7% (PRL, 47.2%; GH, 57.1%; ACTH, 55.6%). Postradiosurgical complications were seen in 6%. CONCLUSION: Gamma knife radiosurgery is safe and effective in controlling the tumor growth and improving endocrinological abnormality of pituitary adenoma.

25.

**Year:** 2003

**Patient number:** 30

**Author:** Attanasio, Roberto; Epaminonda, Paolo; Motti, Enrico; Giugni, Enrico; Ventrella, Laura; Cozzi, Renato; Farabola, Mario; Loli, Paola; Beck, Peccoz Paolo; Arosio, Maura

**Reference:** The Journal of clinical endocrinology and metabolism, 88, 7, 3105-12, 2003

**Title:** Gamma-knife radiosurgery in acromegaly: a 4-year follow-up study

**Abstract:** 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

26.

**Year:** 2003

**Patient number:** 42

**Author:** Choi, Jae Young; Chang, Jong Hee; Chang, Jin Woo; Ha, Yoon; Park, Yong Gou; Chung, Sang Sup

**Reference:** Yonsei medical journal, 44, 4, 602-7, 2003

**Title:** Radiological and hormonal responses of functioning pituitary adenomas after

gamma knife radiosurgery

**Abstract:**In this study, we examined patients with functioning pituitary adenoma that underwent Gamma Knife radiosurgery (GKS). In particular, we assessed the effects of GKS on the growth and endocrinological response of the functioning pituitary adenoma. Forty-two cases of functioning pituitary adenoma treated with GKS were analyzed. The mean follow-up duration was 42.5 months (range 6 - 98), and the mean tumor volume was 1.4 cm<sup>3</sup> (range 0.1 - 3.8). Multiple isocenters, ranging from 1 to 6 in number (mean 2.7), were used. The tumor margin was covered by an isodose ranging from 50 to 90%. The margin dose was 18 to 40 Gy (mean 28.5) and the maximum dose varied from 35 to 80 Gy (mean 54.1). Tumor growth was controlled in 96.9% of the cases and tumor shrinkage occurred in 40.6% of the cases. Hormonal response was observed in 35 of the 42 (83.3%) patients after GKS, with a mean duration of 6.8 months. Sixteen of the 42 (38.1%) patients showed hormonal normalization, with a mean duration of 21 months. In our multivariate analysis, high integral dosage (p=0.005) and maximum dosage (p=0.001) correlated significantly with hormonal normalization. For patients with functioning pituitary adenoma, GKS can be effective in controlling tumor growth and inducing hormonal normalization, especially if patients are reluctant to undergo surgical resection, or are not able to undergo microsurgery under general anesthesia. It appears that early hormonal normalization can be induced by high maximum dosage (at least 50 Gy) and broad coverage of the target volume within the isodose curve, while keeping the maximum dose to the visual pathways below 9 Gy.

27.

**Year:** 2003

**Patient number:** 11

**Author:** Degerblad, M.; Brismar, K.; Rähn, T.; Thorén, M.

**Reference:** Journal of internal medicine, 253, 4, 454-62, 2003

**Title:** The hypothalamus-pituitary function after pituitary stereotactic radiosurgery: evaluation of growth hormone deficiency

**Abstract:****OBJECTIVES:** Radiation therapy to the pituitary gland means a considerable risk of developing hypopituitarism. The aim of the study was to investigate the growth hormone releasing hormone (GHRH)-growth hormone (GH)-insulin-like growth factor-I (IGF-I) axis after treatment with stereotactic radiosurgery to the pituitary because of Cushing's disease. **SETTING:** Inpatient ward in university clinic. **SUBJECTS:** Eleven adult patients (eight women, three men), 20-65 years of age were studied 2.5-11.3 years after stereotactic radiosurgery (isocentre dose 50-100 Gy lesion-1) and compared with healthy controls. **MAIN OUTCOME MEASURES:** Spontaneous GH secretion was evaluated as 12-h night GH profiles. Stimulated GH responses were evaluated in seven of 11 patients using arginine-insulin and GHRH tests. Serum IGF-I levels were measured in fasting serum morning samples. **RESULTS:** All patients except one displayed blunted nocturnal GH profiles. After arginine-insulin challenge, six of seven patients displayed low GH release. GH response was higher after GHRH injection compared with both the response to arginine-insulin and to the maximum GH levels in the nocturnal profiles. Seven patients had an IGF-I standard deviation score (SDS) within the normal range for

age. Serum IGF-I values were correlated to mean GH values in the 12-h night profile ( $r = 0.67$ ,  $P < 0.05$ ) and both these variables were negatively correlated to time elapse since last radiation treatment ( $r = -0.64$ ,  $P < 0.05$  and  $r = -0.78$ ,  $P < 0.05$ , respectively).  
**CONCLUSIONS:** Our patients with Cushing's disease evaluated several years after stereotactic radiosurgery as the primary and only treatment, demonstrated severely blunted spontaneous GH secretion and GH response to arginine-insulin. A disturbed regulation at the hypothalamic level was suggested as mechanism for this. Noteworthy is that serum IGF-I values correlated to the mean values of the 12-h GH profile.

28.

**Year:** 2003

**Patient number:** 142

**Author:** Jane, John A., Jr.; Vance, Mary Lee; Woodburn, C. J.; Laws, Edward R., Jr.

**Reference:** Neurosurgical focus (electronic resource), {Neurosurg-Focus}, 15 May 2003 (epub), vol. 14, no. 5, p. e12, ISSN: 1092-0684.

**Title:** Stereotactic radiosurgery for hypersecreting pituitary tumors: part of a multimodality approach

**Abstract:** OBJECT: Surgical and medical therapies successfully achieve biochemical remission in the majority of patients with secretory pituitary adenomas. Nevertheless, continued hypersecretion after first-line therapy occurs and requires adjunctive therapy to prevent morbidity and premature mortality. For patients in whom medical and surgical therapy have failed, gamma knife surgery (GKS) is performed with the goal of controlling tumor growth and excess growth hormone (GH) production. The authors report their experience with GKS in patients in whom surgical and medical therapies failed.

**METHODS:** The neuroendocrine service at the University of Virginia has treated 220 patients with secretory adenomas. The authors evaluated the biochemical results in patients with acromegaly followed for greater than 18 months (64 patients) as well as those with Cushing disease (45 patients), Nelson syndrome (14 patients with adequate follow up (27 overall)), and prolactinomas (19 patients) followed for at least 12 months posttreatment. Biochemical remission occurred in 36% of patients with GH-secreting adenomas, 73% of those with Cushing disease, 14% of those with Nelson syndrome, and 11% of those harboring prolactinomas. Recurrence after biochemical remission was documented in four patients with Cushing disease. New hormonal deficits have occurred in 28% of patients with acromegaly, 31% with Cushing disease, 36% with Nelson syndrome, and 21% with prolactinomas. Minor visual deterioration developed in one patient with Cushing disease. **CONCLUSIONS:** Gamma knife surgery offers an important treatment modality in patients with secretory adenomas refractory to surgical and medical interventions.

29.

**Year:** 2003

**Patient number:** 28

**Author:** Kondziolka, D.; Nathoo, N.; Flickinger, J. C.; Niranjan, A.; Maitz, A. H.; Lunsford, L. D.; Piepmeyer, J. M.; Berger, M. S.; Loeffler, J. S.; Gutin, P. H.

**Reference:** Neurosurgery, 53, 4, 815-822, 2003

**Title:** Long-term results after radiosurgery for benign intracranial tumors

**Abstract:**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.

30.

**Year:** 2003

**Patient number:** 78

**Author:** Petrovich, Zbigniew; Yu, Cheng; Giannotta, Steven L.; Zee, Chi Shing; Apuzzo, Michael L. J.

**Reference:** Neurosurgery, 53, 1, 51-9, 2003

**Title:** Gamma knife radiosurgery for pituitary adenoma: early results

**Abstract:**OBJECTIVE: In recent years, gamma knife radiosurgery (GKRS) has emerged as an important treatment modality in the management of pituitary adenomas. Treatment results after performing GKRS and the complications of this procedure are reviewed. METHODS: Between 1994 and 2002, a total of 78 patients with pituitary adenomas underwent a total of 84 GKRS procedures in our medical center. This patient group comprised 46 men (59%) and 32 women (41%). All patients were treated for recurrent or residual disease after surgery or radiotherapy, with 83% presenting with extensive tumor involvement. The cavernous sinus was involved in 75 patients (96%), and 22 patients (28%) had hormone-secreting adenomas. This latter subset of patients included 12 prolactinomas (15%), 6 growth-hormone secreting tumors (8%), and 4

adrenocorticotrophic hormone-secreting tumors (5%). The median tumor volume was 2.3 cm<sup>3</sup>, and the median radiation dose was 15 Gy defined to the 50% isodose line. The mean and median follow-up periods were 41 and 36 months, respectively. **RESULTS:** GKRS was tolerated well in these patients; acute toxicity was uncommon and of no clinical significance. Late toxicity was noted in three patients (4%) and consisted of VIth cranial nerve palsy. In two patients, there was spontaneous resolution of this palsy, and in one patient, it persisted for the entire 3-year duration of follow-up. Of the 15 patients who presented with cranial nerve dysfunction, 8 (53%) experienced complete recovery and 3 (20%) showed major improvement within 12 months of therapy. Tumor volume reduction was slow, with 30% of patients showing decreased tumor volume more than 3 years after undergoing GKRS. None of the 56 patients with nonfunctioning tumors showed progression in the treated volume, and 4 (18%) of the 22 hormone-secreting tumors relapsed ( $P = 0.008$ ). Of the four patients with adrenocorticotrophic hormone-secreting adenomas, therapy failed in two of them. All six patients with growth hormone-producing tumors responded well to therapy. Of the 12 patients with prolactinomas 10 (83%) had normalization of hormone level and 2 patients experienced increasing prolactin level. Two patients with prolactinomas had three normal pregnancies after undergoing GKRS. **CONCLUSION:** GKRS is a safe and effective therapy in selected patients with pituitary adenomas. None of the patients in our study experienced injury to the optic apparatus. A radiation dose higher than 15 Gy is probably needed to improve control of hormone-secreting adenomas. Longer follow-up is required for a more complete assessment of late toxicity and treatment efficacy.

31.

**Year:** 2003

**Patient number:** 33

**Author:** Pollock, B. E.; Carpenter, P. C.; Kondziolka, D.; Post, K. D.; King, W.; Tabar, V.; Loeffler, J. S.; Laws, Jr E. R.; Adler, Jr J. R.

**Reference:** Neurosurgery, 53, 5, 1086-1094, 2003

**Title:** Stereotactic Radiosurgery as An Alternative to Fractionated Radiotherapy for Patients with Recurrent or Residual Nonfunctioning Pituitary Adenomas

**Abstract:** **OBJECTIVE:** To evaluate tumor control rates and complications after stereotactic radiosurgery for patients with nonfunctioning pituitary adenomas.

**METHODS:** Between 1992 and 2000, 33 patients underwent radiosurgery for treatment of nonfunctioning pituitary adenomas. Thirty-two patients (97%) had undergone one or more previous tumor resections. Twenty-two patients (67%) had enlarging tumors before radiosurgery. The median tumor margin dose was 16 Gy (range, 12-20 Gy). The median follow-up period after radiosurgery was 43 months (range, 16-106 mo). **RESULTS:** Tumor size decreased for 16 patients, remained unchanged for 16 patients, and increased for 1 patient. The actuarial tumor growth control rates at 2 and 5 years after radiosurgery were 97%. No patient demonstrated any decline in visual function. Five of 18 patients (28%) with anterior pituitary function before radiosurgery developed new deficits, at a median of 24 months after radiosurgery. The actuarial risks of developing new anterior pituitary deficits were 18 and 41% at 2 and 5 years, respectively. No patient developed diabetes

insipidus. **CONCLUSION:** Stereotactic radiosurgery safely provides a high tumor control rate for patients with recurrent or residual nonfunctioning pituitary adenomas. However, despite encouraging early results, more long-term information is needed to determine whether radiosurgery is associated with lower risks of new endocrine deficits and radiation-induced neoplasms, compared with fractionated radiotherapy.

32.

**Year:** 2003

**Patient number:** 46

**Author:** Sheehan, Jason P.; Kondziolka, Douglas; Flickinger, John; Lunsford, L. Dade

**Reference:** Neurosurgical focus (electronic resource), {Neurosurg-Focus}, 15 May 2003 (epub), vol. 14, no. 5, p. e9, ISSN: 1092-0684.

**Title:** Radiosurgery for nonfunctioning pituitary adenoma

**Abstract:** **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.

33.

**Year:** 2003

**Patient number:** 34

**Author:** Shin, M.; Kurita, H.; Kirino, T.

**Reference:** Japanese Journal of Neurosurgery, 12, 5, 337-342, 2003

**Title:** Gamma knife radiosurgery for pituitary adenomas: Indications and treatment outcomes

**Abstract:** For the treatment of pituitary adenomas, transsphenoidal surgery is established as a first choice of treatment. However, pituitary adenomas are occasionally not curable by surgery alone, when they extend into the cavernous sinus or are found in the patients

with poor physical conditions. Here we present our experience with stereotactic radiosurgery using a gamma knife in the treatment of 34 pituitary adenomas. There were 3 non-functioning adenomas and 31 functioning; 17 growth hormone (GH) and 14 adrenocorticotrophic hormone (ACTH) adenomas. The mean radiation dose delivered to the tumor margin was 16 Gy and 32.1 Gy for non-functioning tumors and functioning tumors, respectively, while keeping the dose to the optic pathway below 10 Gy. With a median follow-up of 3 years, tumor growth control was achieved in all cases. In GH producing tumors, 8 of 16 evaluated cases were endocrinologically improved; serum GH < 5 ng/ml, the insulin like growth factor-1 (IGF-1) < 450 ng/ml, and the remaining 5 cases also showed a steady decrease of the GH and IGF-1 level. In ACTH producing tumors, 7 of 11 cases were endocrinologically normalized (< 90 (mu)g/day 24 hour urinary free cortisol). One patient showed permanent hypopituitarism, and another one presented with abducens nerve palsy more than 5 years after radiosurgery. Gamma knife radiosurgery is a safe treatment modality for pituitary adenomas, with an effectiveness equivalent to conventional radiation therapy but with much less risk of radiation injury to the surrounding structures. Longer follow-up data with a further accumulation of cases is essential, but our experience reported here will contribute to establish a radiosurgical protocol for these tumors.

34.

**Year:** 2003

**Patient number:** 89

**Author:** Stafford, Scott L.; Pollock, Bruce E.; Leavitt, Jacqueline A.; Foote, Robert L.; Brown, Paul D.; Link, Michael J.; Gorman, Deborah A.; Schomberg, Paula J.

**Reference:** International journal of radiation oncology biology physics, 55, 5, 1177-81, 2003

**Title:** A study on the radiation tolerance of the optic nerves and chiasm after stereotactic radiosurgery

**Abstract:** **PURPOSE:** To evaluate the risk of clinically significant radiation optic neuropathy (RON) for patients having stereotactic radiosurgery of benign tumors adjacent to the optic apparatus. **METHODS AND MATERIALS:** We reviewed the dose plans and clinical outcomes of 218 gamma knife procedures (215 patients) for tumors of the sellar and parasellar region (meningiomas, n = 122; pituitary adenomas, n = 89; craniopharyngiomas, n = 7 patients). Previous surgery or radiation therapy was performed in 156 (66%) and 24 (11%) patients, respectively. Median follow-up was 40 months (range 4-115). **RESULTS:** The median maximum radiation dose to the optic nerve was 10 Gy (range 0.4-16.0). Four patients (1.9%) developed RON at a median of 48 months after radiosurgery. All had prior surgery, and 3 of 4 had external beam radiotherapy (EBRT) in their management either before (n = 2) or adjuvantly (n = 1). The risk of developing a clinically significant RON was 1.1% for patients receiving 12 Gy or less. Patients receiving prior or concurrent EBRT had a greater risk of developing RON after radiosurgery (p = 0.004). **CONCLUSION:** RON occurred in less than 2% of our patients, despite the majority (73%) receiving more than 8 Gy to a short segment of the optic apparatus. Knowledge of the dose tolerance of these structures permits physicians

to be more aggressive in treating patients with sellar or parasellar tumors, especially those with hormone-producing pituitary adenomas that appear to require higher doses to achieve biochemical remission.

35.

**Year:** 2003

**Patient number:** 149

**Author:** Wang, Mei hua; Liu, Peng; Liu, A. li; Luo, Bin; Sun, Shi bin

**Reference:** Zhonghua yi xue za zhi, 83, 23, 2045-8, 2003

**Title:** Efficacy of gamma knife radiosurgery in treatment of growth hormone- secreting pituitary adenoma

**Abstract:**OBJECTIVE: To evaluate the efficacy of gamma knife radiosurgery (GKS) in treatment of growth hormone (GH)-secreting pituitary adenoma. METHODS: 149 patients with GH-secreting pituitary adenoma, 97 males and 52 females, aged 42.8 (12-72 years), with a course of 6-240 months (72.5 months) and with the mean volume of tumor of 2.36 cm<sup>3</sup> (0.11-12.7 cm<sup>3</sup>) were treated by GKS. The mean dose to tumor margin was 20.87 Gy (10-30 Gy). 124 of them were followed up for 30 months (6-72 months). RESULTS: The serum GH returned normal in 74 patients (64.9%) and declined in comparison with the level before radiosurgery in 23 patients (18.5%). The tumor volume was reduced in 84 patients (67.7%) and remained unchanged in 124 patients (32.4%). Ambliopia appeared in one patient. No other complication was found during the follow-up. CONCLUSION: GKS is safe and effective on the treatment of

36.

**Year:** 2003

**Patient number:** 63

**Author:** Vladyka, Vilibald; Liscák, Roman; Novotn<sup>3</sup>, Josef, Jr.; Marek, Josef; Jezková, Jana

**Reference:** Neurosurgery, 52, 2, 309-16, 2003

**Title:** Radiation tolerance of functioning pituitary tissue in gamma knife surgery for pituitary adenomas

**Abstract:**OBJECTIVE: This study is intended to contribute to a determination of the sensitivity of preserved hypophyseal function to focal radiation in pituitary adenomas. METHODS: We compared two subgroups of patients followed up for a median of 5 years after gamma knife surgery (GKS). Subgroup 1 (n = 30) showed postirradiation hypopituitarism. Subgroup 2 (n = 33) was continually eupituitary. These subgroups were taken from a previously published study relating to a larger group of 163 patients with pituitary adenomas treated by GKS and evaluated after a median follow-up period of 2 years. A relatively high treatment dose was used in this larger group (median, 20 Gy to the tumor margin for growth control in nonfunctioning adenomas; median, 35 Gy for hypersecreting adenomas). Early results approached those of microsurgery, and there were only a few side effects. In the present study, we compared 16 different variables in

the same two subgroups to discover the relationships that caused a delayed appearance of postirradiation hypopituitarism. The main pretreatment and treatment parameters were measured on reconstructed treatment plans. This database was used for statistical evaluation. RESULTS: The relationship between the mean dose and the volume of functioning hypophysis was stronger in terms of worsening of pituitary function than that of the spot dose to different intrasellar structures. We found that for our group of patients, the safe mean dose of radiation to the hypophysis was 15 Gy for gonadotropic and thyrotropic functions and 18 Gy for adrenocorticotrophic function. The worsening of pituitary function was also significantly dependent on the dose to different anatomic levels of the infundibulum, but we did not succeed in fully characterizing this relationship. In addition, we discovered significant levels of dependency of postirradiation pituitary damage to different pretreatment and treatment variables. CONCLUSION: Knowledge of the radiation tolerance of functioning pituitary structures subjected to GKS can ensure better preservation of pituitary function after irradiation. This is valid for the group of patients we studied. Our study's findings can be used as a guideline for GKS treatment of new patients with pituitary adenomas, and it can serve for comparison with the experience of other gamma knife centers.

37.

**Year:** 2002

**Patient number:** 92

**Author:** Feigl, Gunther Christian; Bonelli, Christine Maria; Berghold, Andrea; Mokry, Michael

**Reference:** Journal of neurosurgery, 97, 5Suppl, 415-21, 2002

**Title:** Effects of gamma knife radiosurgery of pituitary adenomas on pituitary function

**Abstract:** OBJECT: The authors undertook a retrospective analysis of the incidence and time course of pituitary insufficiency following gamma knife radiosurgery (GKS) for pituitary adenomas. METHODS: Pituitary adenomas in 92 patients were analyzed. There were 61 hormonally inactive tumors, 18 prolactinomas, and nine somatotrophic and four adrenocorticotrophic adenomas. The mean tumor volume was 3.8 cm<sup>3</sup> (range 0.2-14.6 cm<sup>3</sup>). The mean prescription dose was 15 Gy. The mean prescription isodose was 50.7%. The mean follow-up time was 4.6 years (range 1.2-10 years). The following new or deteriorating insufficiencies that did not require treatment were recorded for the different pituitary axes: follicle-stimulating hormone (FSH)/ luteinizing hormone (LH) 19 (20.6%), thyroid-stimulating hormone (TSH) 32 (34.8%), adrenocorticotrophic hormone (ACTH) 10 (10.9%), and growth hormone (GH) 26 (28.3%). For new insufficiencies or deterioration requiring replacement therapy, the figures were as follows: FSH/LH 20 (21.7%), TSH 22 (23.9%), ACTH eight (8.7%), and GH 12 (13%). Spot dosimetry was performed in 59 patients in the hypothalamic region, the pituitary gland, and pituitary stalk. The pituitary stalks in patients with deterioration of pituitary function received a statistically higher dosage of radiation, 7.7 +/- 3.7 Gy compared with 5.5 +/- 3 Gy (p = 0.03).

CONCLUSIONS: The function of the residual normal pituitary gland is less affected following GKS of pituitary adenomas than after fractionated radiotherapy. Nonetheless, increased attention needs to be exercised to reduce the dose to the stalk and pituitary

gland to minimize the incidence of these complications.

38.

**Year:** 2002

**Patient number:** 25

**Author:** Kobayashi, Tatsuya; Kida, Yoshihisa; Mori, Yoshimasa

**Reference:** Journal of neurosurgery, 97, 5Suppl, 422-8, 2002

**Title:** Gamma knife radiosurgery in the treatment of Cushing disease: long-term results  
**Abstract:**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 adrenocorticotrophic 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.

39.

**Year:** 2002

**Patient number:** 43

**Author:** Pollock, B. E.; Nippoldt, T. B.; Stafford, S. L.; Foote, R. L.; Abboud, C. F.

**Reference:** Journal of Neurosurgery, 97, 3, 525-530, 2002

**Title:** Results of stereotactic radiosurgery in patients with hormone-producing pituitary adenomas: Factors associated with endocrine normalization

**Abstract:**Object. The goal of this study was to determine factors associated with endocrine normalization after radiosurgery is performed in patients with hormone-producing pituitary adenomas. Methods. Between 1990 and 1999, 43 patients with hormone-producing pituitary adenomas underwent radiosurgery: 26 patients with growth hormone (GH)-producing tumors, nine with adrenocorticotrophic

hormone-producing tumors, seven with tumors that produced prolactin (PRL) alone, and one with a tumor that secreted both GH and PRL. The median patient age was 42 years. Thirty-seven patients (86%) had undergone surgery earlier and in 30 (70%) there was tumor extension into the cavernous sinus. The product-limit method was used to calculate endocrine normalization while patients were not receiving any hormone-suppressive medication. The median follow-up period after radio-surgery was 36 months (range 12-108 months). In 20 patients (47%) there was normalization of hormone secretion at a median of 14 months (range 2-44 months) after radiosurgery; no correlation was found between tumor type and cure. Actuarial cure rates were 20, 32, and 61% at 1, 2, and 4 years posttreatment. Multivariate analysis demonstrated that the absence of hormone-suppressive medications at the time of radiosurgery (relative risk 8.9, 95% confidence interval (CI) 1.2-68.7,  $p = 0.04$ ) and maximum radiation doses greater than 40 Gy (relative risk 3.9, 95% CI 1.3-11.7,  $p = 0.02$ ) correlated with an endocrine cure. A new anterior pituitary deficiency developed in seven patients (16%), temporal lobe necrosis was identified in two patients, an asymptomatic internal carotid artery stenosis was detected in two patients, and unilateral blindness occurred in one patient. Conclusions. Radiosurgery provides an endocrine cure for many patients with persistent or recurrent hormone-producing pituitary adenomas. Further study is needed to determine whether pituitary hormone-suppressive medications have a radioprotective effect.

40.

**Year:** 2002

**Patient number:** 11

**Author:** Pollock, Bruce E.; Young, William F., Jr.

**Reference:** International journal of radiation oncology biology physics, 54, 3, 839-41, 2002

**Title:** Stereotactic radiosurgery for patients with ACTH-producing pituitary adenomas after prior adrenalectomy

**Abstract:** PURPOSE: To review the results of stereotactic radiosurgery for patients with adrenocorticotrophic hormone (ACTH)-producing pituitary adenomas after bilateral adrenalectomy. METHODS AND MATERIALS: Eleven patients with ACTH-producing pituitary adenomas after bilateral adrenalectomy underwent radiosurgery between 1990 and 1999. Nine patients had documented tumor growth, hyperpigmentation, and elevated ACTH levels (median 920 ng/mL) at the time of radiosurgery. Five of these patients had tumor enlargement despite prior fractionated radiotherapy (median dose 50 Gy). Two patients were treated prophylactically within 1 month of their adrenalectomies to prevent future tumor growth. The median follow-up was 37 months (range 22-74). RESULTS: Tumor growth control was achieved in 9 patients (82%); 2 patients had had continued tumor growth after radiosurgery. The ACTH levels decreased a median of 66% (range -99% to +27%); 4 patients had normal ACTH levels. Three patients had radiation-related complications, including diplopia ( $n = 2$ ), ipsilateral blindness ( $n = 1$ ), testosterone/growth hormone deficiency ( $n = 1$ ), and asymptomatic temporal lobe radiation necrosis ( $n = 1$ ): all had received prior radiotherapy. One patient who had undergone three prior resections

and radiotherapy died 59 months after radiosurgery despite two additional attempts at tumor resection. **CONCLUSION:** Although our experience is limited, it appears that radiosurgery provides tumor control for most patients with ACTH-producing pituitary adenomas who have undergone bilateral adrenalectomy.

41.

**Year:** 2002

**Patient number:** 42

**Author:** Sheehan, Jason P.; Kondziolka, Douglas; Flickinger, John; Lunsford, L. Dade

**Reference:** Journal of neurosurgery, 97, 5Suppl, 408-14, 2002

**Title:** Radiosurgery for residual or recurrent nonfunctioning pituitary adenoma

**Abstract:****OBJECT:** Nonfunctioning pituitary adenomas comprise approximately 30% of all pituitary tumors. The purpose of this retrospective study is to evaluate the efficacy and role of gamma knife radiosurgery (GKS) in the management of residual or recurrent nonfunctioning pituitary adenomas. **METHODS:** A review was conducted of the data obtained in 42 patients who underwent adjuvant GKS at the University of Pittsburgh between 1987 and 2001. Prior treatments included transsphenoidal resection, craniotomy and resection, or conventional radiotherapy. Endocrinological, ophthalmological, and radiological responses were evaluated. The duration of follow-up review varied from 6 to 102 months (mean 31.2 months). Fifteen patients were observed for more than 40 months. The mean radiation dose to the tumor margin was 16 Gy. Conformal radiosurgery planning was used to restrict the dose to the optic nerve and chiasm. Tumor control after GKS was achieved in 100% of patients with microadenomas and 97% of patients with macroadenomas. Gamma knife radiosurgery was equally effective in controlling adenomas with cavernous sinus invasion and suprasellar extension. No patient developed a new endocrinological deficiency following GKS. One patient's tumor enlarged with an associated decline in visual function. Another patient experienced a deterioration of visual fields despite a decrease in tumor size. **CONCLUSIONS:** Gamma knife radiosurgery can achieve tumor control in virtually all residual or recurrent nonfunctioning pituitary adenomas. Dose sparing facilitates tumor management even when the adenoma is close to the optic apparatus or invades the cavernous sinus.

42.

**Year:** 2002

**Patient number:** 30

**Author:** Wowra, Berndt; Stummer, Walter

**Reference:** Journal of neurosurgery, 97, 5Suppl, 429-32, 2002

**Title:** Efficacy of gamma knife radiosurgery for nonfunctioning pituitary adenomas: a quantitative follow up with magnetic resonance imaging- based volumetric analysis

**Abstract:****OBJECT:** The authors assessed the efficacy of gamma knife radiosurgery (GKS) for nonfunctioning pituitary adenomas (NPAs) by sequential quantitative

determinations of tumor volume and neurological and endocrinological follow-up examinations. **METHODS:** Through May of 2000, 45 patients with NPA were treated by GKS. Complete neurological and endocrinological follow-up information was obtained. In 30 patients (67%), follow-up examinations included stereotactic magnetic resonance imaging involving the GammaPlan software for sequential measurements of the NPA volume. These patients constitute the basis of this study. Sequential volume measurements after GKS were compared with initial tumor volumes at the date of GKS to quantify the therapeutic result. All data were stored prospectively in a computerized database. The median dose to the tumor margin was 16 Gy (range 11-20 Gy). The mean prescription isodose was 55% (range 45-75%). All except one patient (97%) underwent surgery for NPA before GKS. Fractionated radiotherapy was not administered. Median follow up after GKS was 55 months (range 28-86 months). The actuarial long-term recurrence-free survival was 93% with respect to a single GKS and 100% if a repeated GKS was included. Neurological side effects were not detected. The actuarial risk of radiosurgery-induced pituitary damage was calculated to be 14% after 6 years. The volumetric analysis revealed a temporary swelling of the NPA in four patients, followed by shrinkage of the lesion. This is the first time this has been observed in pituitary adenomas. **CONCLUSIONS:** Postoperative GKS for residual or recurrent small fragments of NPAs is effective and safe. With regard to the issues of radioprotection and therapeutic morbidity, it seems superior to fractionated radiotherapy. Quantification of tumor reduction is a valuable tool for documenting a therapeutic response and for identifying tumor recurrence. As part of a radiosurgical standard protocol, the follow-up examination for NPAs should include tumor volumetric analysis.

43.

**Year:** 2001

**Patient number:** 29

**Author:** Chen, J. C.; Giannotta, S. L.; Yu, C.; Petrovich, Z.; Levy, M. L.; Apuzzo, M. L.

**Reference:** Neurosurgery, 48, 5, 1022-30, 2001

**Title:** Radiosurgical management of benign cavernous sinus tumors: dose profiles and acute complications

**Abstract:** **OBJECTIVE:** Radiosurgery has emerged as an alternative treatment modality for cranial base tumors in patients deemed not suited for primary surgical extirpation, patients with recurrent or residual tumor after open surgery, or patients who refuse surgical treatment. We review our short-term experience with radiosurgical management of cavernous sinus region tumors with the Leksell gamma knife. **METHODS:** From August 1994 to February 1999, 69 patients with cavernous sinus lesions were treated in 72 separate treatment sessions. The tumor type distribution was 29 pituitary adenomas, 35 meningiomas, 4 schwannomas, and 1 paraganglioma. The median follow-up was 122 weeks. Lesions were stratified according to a five-level surgical grade. The grade distribution of the tumors was as follows: Grade I, 13; Grade II, 21; Grade III, 19; Grade IV, 12; Grade V, 4. Median tumor volume was 4.7 cm<sup>3</sup>. The median radiation dose was 15 Gy to the 50% isodose line. Median maximal radiation dose was 30 Gy. **RESULTS:** Analysis of tumor characteristics and radiation dose to optic nerve and pontine structures

revealed a significant correlation between distance and dose. Much lower correlation coefficients were found between tumor volume and dose. One lesion in this series had evidence of transient progression and later regression on follow-up radiographic studies. No other lesions in this series were demonstrated to have exhibited progression. Complications after radiosurgical treatment were uncommon. Two patients had cranial nerve deficits after treatment. One patient with a surgical Grade III pituitary adenoma had VIth cranial nerve palsy 25 months after radiosurgical treatment that spontaneously resolved 10 months later. A patient with a bilateral pituitary adenoma experienced bilateral VIth cranial nerve palsy 3 months after treatment that had not resolved at 35 months after treatment. Six patients with preoperative cranial nerve deficits experienced resolution or improvement of their deficits after treatment. One patient with a prolactin-secreting adenoma experienced normalization of endocrine function with return of menses. **CONCLUSION:** Radiosurgical treatment represents an important advance in the management of cavernous sinus tumors, with low risk of neurological deficit in comparison with open surgical treatment, even in patients with high surgical grades.

44.

**Year:** 2001

**Patient number:** 89

**Author:** Höybye, C.; Grenbäck, E.; Råhn, T.; Degerblad, M.; Thorén, M.; Hulting, A. L.

**Reference:** Neurosurgery, 49, 2, 284-91, 2001

**Title:** Adrenocorticotrophic hormone-producing pituitary tumors: 12- to 22-year follow-up after treatment with stereotactic radiosurgery

**Abstract:** **OBJECTIVE:** To study retrospectively long-term outcomes of patients with adrenocorticotrophic hormone-producing pituitary tumors that were treated with stereotactic Leksell gamma knife unit radiosurgery. **METHODS:** Eighty-nine patients aged 5 to 67 years were treated between 1976 and 1985. Eighteen patients aged 18 to 68 years (mean age, 41 yr) were followed in detail. Fifteen patients were women. None had previously received conventional radiotherapy, but pituitary microsurgery had been performed in two patients, and one patient had had an adrenalectomy. In the remaining 15 patients, radiosurgery was the primary therapy. **RESULTS:** Sixty-four patients had one stereotactic treatment, and 25 patients had two or more treatments. No complications were observed during treatment and the immediate follow-up period. At follow-up, 17 patients had died 1 to 20 years after the first treatment. No deaths were related to the treatment. In our 18 patients, the follow-up time after the first radiosurgical treatment was 12 to 22 years (mean follow-up period, 17 yr). Urinary cortisol levels gradually normalized in 83% of the patients. No recurrences were observed. Pituitary hormone insufficiencies developed in about two of every three patients and occurred even more than 10 years after treatment. Eight patients had transient hyperprolactinemia. The patients' vision and visual fields were unaffected, and none of them had signs of radiation-induced side effects such as brain tumors or brain necrosis. **CONCLUSION:** Stereotactic radiosurgery is a safe and effective method in the treatment of patients with adrenocorticotrophic hormone-producing pituitary tumors, and the effect of treatment is long-lasting. Stereotactic radiosurgery is mainly a complement to microsurgery because of its

gradually appearing effect and the occurrence of pituitary insufficiency. New pituitary deficiencies may be found more than 10 years after treatment.

45.

**Year:** 2001

**Patient number:** 44

**Author:** Tung, G. A.; Noren, G.; Rogg, J. M.; Jackson, I. M.

**Reference:** AJR. American journal of roentgenology, 177, 4, 919-24, 2001

**Title:** MR imaging of pituitary adenomas after gamma knife stereotactic radiosurgery

**Abstract:**OBJECTIVE: The purpose of this study was to evaluate the response of pituitary adenomas to radiosurgery as manifested by changes in size and appearance on serial MR imaging. MATERIALS AND METHODS: Over a mean follow-up period of 36 months, changes in 44 pituitary adenomas were assessed on 147 enhanced MR imaging studies. Prior surgery had been performed in 36 tumors (82%). RESULTS: At the time of radiosurgery, mean tumor volume was 5.9 +/- 0.8 cm<sup>3</sup> (mean diameter, 2.2 cm). The mean reduction in volume at last follow-up was 41% (+/- 5%, p < 0.001), and a decrease in tumor volume of 25-100% was observed in 34 tumors (77%). Mean reduction in tumor volume at 6 months after radiosurgery was 9% (p = 0.095); at 1 year, 24% (p < 0.001); at 2 years, 34% (p < 0.001); at 3 years, 41% (p < 0.001); and at 4 years, 50% (p = 0.008). Six months after radiosurgery a slight and transient increase in size was observed in 21% of tumors. During follow-up, neither decreased contrast enhancement nor cyst development was associated with changes in tumor volume. CONCLUSION: Tumor control was observed for most pituitary adenomas after radiosurgery and occurred gradually over a period of several years. A small increase in tumor size might be observed in the first 6 months after radiosurgery. In most cases, reductions in tumor size were not accompanied by a change in contrast enhancement or cyst formation.

46.

**Year:** 2000

**Patient number:** 74

**Author:** Izawa, M.; Hayashi, M.; Nakaya, K.; Satoh, H.; Ochiai, T.; Hori, T.; Takakura, K.

**Reference:** Journal of neurosurgery, 93, Suppl 3, 19-22, 2000

**Title:** Gamma knife radiosurgery for pituitary adenomas

**Abstract:**OBJECT: The purpose of this study was the analysis of a large series of patients treated with gamma knife radiosurgery for pituitary adenoma in a single institution. METHODS: One hundred eight patients with pituitary adenomas were treated over the last 7 years. Seventy-four patients have been followed for more than 6 months and form the basis of this report. CONCLUSIONS: Twenty-three patients harbored nonfunctioning adenomas, and 56 harbored functioning adenomas. The mean margin dose was 22.5 Gy (nonfunctioning adenomas, 19.5 Gy; functioning adenomas, 23.8 Gy). Control of tumor growth was achieved in 91%. A significant decrease of excessive hormone production was seen in 80% of patients, and the endocrinological normalization

rate was 30.3%. Postradiosurgical complications were seen in 2.5%.

47.

**Year:** 2000

**Patient number:** 33

**Author:** Landolt, A. M.; Haller, D.; Lomax, N.; Scheib, S.; Schubiger, O.; Siegfried, J.; Wellis, G.

**Reference:** The Journal of clinical endocrinology and metabolism, 85, 3, 1287-9, 2000

**Title:** Octreotide may act as a radioprotective agent in acromegaly

**Abstract:** Clinical experience shows that an increasing number of patients undergoing radiation treatment for recurring acromegaly or acromegaly persisting after surgery are treated with octreotide. We, therefore, performed a follow-up study of patients undergoing stereotactic radiosurgery (Gamma Knife) to determine whether this medication has an influence on the ultimate result of radiation therapy in either a positive or negative sense. It has been suggested that the combination of radiation with antisecretory drugs may increase the effectiveness of radiation. A follow-up study of 31 patients suffering from recurrent acromegaly and acromegaly persisting after surgery, and who had been treated with stereotactic radiosurgery, showed that patients treated with octreotide at the time of radiation application simultaneously reached a normal level of growth hormone and insulin-like growth factor-I only after a significantly longer interval than patients who did not receive the drug. The two groups of patients did not demonstrate significant differences in the main clinical findings (age, sex, target volume, radiation dose, baseline growth hormone, and baseline insulin-like growth factor-I).

48.

**Year:** 2000

**Patient number:** 20

**Author:** Landolt, A. M.; Lomax, N.

**Reference:** Journal of neurosurgery, 93, Suppl 3, 14-8, 2000

**Title:** Gamma knife radiosurgery for prolactinomas

**Abstract:** OBJECT: In this retrospective investigation the authors examined the results of gamma knife radiosurgery (GKS) for tumor remnants after unsuccessful open surgery and medical treatment in 20 patients with prolactinomas. Particular attention is paid to a possible radioprotective action of dopamine agonists similar to the action of octreotide in acromegaly. METHODS: Twenty patients with prolactinomas were followed after GKS. Five patients were treated successfully; their prolactin (PRL) levels dropped into the normal range and dopaminergic drugs could be discontinued. Two spontaneous pregnancies were observed and 11 patients experienced improvement. Improvement was defined as normal PRL levels with the continued possibility of reduced medical treatment or a substantially reduced medical treatment dose with some degree of hyperprolactinemia maintained. The treatment failed in three patients who experienced no improvement. Patients treated with dopaminergic drugs during GKS did significantly

less well in comparison with the untreated group when a cumulative distribution function (Kaplan-Meier estimate) was used. **CONCLUSIONS:** The results of GKS for prolactinomas in this investigation are better than the results published by others. This may be an effect of case selection because there were no salvage cases in our group of patients. Because a dopamine agonist seemed to induce radioprotection in this series, it is suggested that GKS be performed during an intermission in drug therapy when the dopamine agonist is discontinued.

49.

**Year:** 2000

**Patient number:** 17

**Author:** Ove, R.; Kelman, S.; Amin, P. P.; Chin, L. S.

**Reference:** International journal of cancer. Journal international du cancer, 90, 6, 343-50, 2000

**Title:** Preservation of visual fields after peri-sellar gamma-knife radiosurgery

**Abstract:** Radiosurgical treatment of pituitary and peri-sellar tumors has become an increasingly utilized modality as an alternative to conventional radiotherapy and surgery. Such radiosurgery results in a relatively high dose of radiation to the optic chiasm. The clinical data establishing safe single-fraction doses to the chiasm is immature, although taken together previous literature suggests a recommended maximal dose of 8 Gy. Optic neuropathy, when it occurs, tends to take place within 2 years of treatment. We evaluated the visual fields of 20 sequential patients that received significant doses to the optic chiasm by Gamma-knife radiosurgery. There were 17 cases of pituitary adenoma and 3 cases of meningioma, and two patients refused follow-up testing. Preoperative visual field and cranial nerve examinations were done prior to radiosurgery and in follow-up, with a median follow-up of 24 months. There were no cases of quantitative visual field deficit induced by treatment. No patients developed symptomatic visual deterioration. Radiat. Oncol. Invest. 90:343-350, 2000. 2000 Wiley- Liss, Inc.

50.

**Year:** 2000

**Patient number:** 164

**Author:** Pan, L.; Zhang, N.; Wang, E. M.; Wang, B. J.; Dai, J. Z.; Cai, P. W.

**Reference:** Journal of neurosurgery, 93, Suppl 3, 10-3, 2000

**Title:** Gamma knife radiosurgery as a primary treatment for prolactinomas

**Abstract:** **OBJECT:** The purpose of this study was to estimate the efficacy of gamma knife radiosurgery (GKS) in controlling tumor growth and endocrinopathy associated with prolactinomas. **METHODS:** Between 1993 and 1997, 164 of 469 patients with pituitary adenomas treated by GKS harbored prolactinomas. The dose to the tumor margin ranged from 9 to 35 Gy (mean 31.2 Gy), and the visual pathways were exposed to a dose of less than 10 Gy. The mean tumor diameter was 13.4 mm. The mean follow-up time for 128 cases was 33.2 months (range 6-72 months). Tumor control was observed in all but two

patients who underwent surgery 18 and 36 months, respectively, after GKS. Clinical cure was achieved in 67 cases. Clinical improvement was noted with a decrease in the hyperprolactinemia after GKS. Nonetheless, in 31 (29%) of 108 patients who were followed for more than 2 years no improvement in serum prolactin levels was demonstrated, although this could be normalized by bromocriptine administration after treatment. Nine infertile women became pregnant 2 to 13 months after GKS and all gave birth to normal children. There was no visual deterioration related to GKS. Five women experienced premature menopause. In these patients there was subtotal disappearance of the tumor and an empty sella developed. **CONCLUSIONS:** Gamma knife radiosurgery as a primary treatment for prolactinomas can be safe and effective both for controlling tumor growth and for normalization of prolactin hypersecretion. A higher margin dose ( $\geq 30$  Gy) seemed to be associated with a better clinical outcome. Gamma knife radiosurgery may make prolactinomas more sensitive to the bromocriptine.

51.

**Year:** 2000

**Patient number:** 43

**Author:** Sheehan, J. M.; Vance, M. L.; Sheehan, J. P.; Ellegala, D. B.; Laws, E. R., Jr.

**Reference:** Journal of neurosurgery, 93, 5, 738-42, 2000

**Title:** Radiosurgery for Cushing's disease after failed transsphenoidal surgery

**Abstract:**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.

52.

**Year:** 2000

**Patient number:** 16

**Author:** Shin, M.; Kurita, H.; Sasaki, T.; Tago, M.; Morita, A.; Ueki, K.; Kirino, T.

**Reference:** Journal of neurosurgery, 93, Suppl 3, 2-5, 2000

**Title:** Stereotactic radiosurgery for pituitary adenoma invading the cavernous sinus

**Abstract:**OBJECT: The purpose of this study is to determine the efficacy of gamma knife radiosurgery (GKS) treatment of pituitary adenomas that have invaded the cavernous sinus. METHODS: Sixteen patients were treated with GKS: three with nonfunctional adenomas and 13 with hormone-secreting (seven growth hormone (GH) and six adrenocorticotrophic hormone (ACTH)) adenomas. More than 16 Gy and 30 Gy were delivered to the tumor margin for nonfunctioning tumors and functioning tumors, respectively, keeping the dose to the optic pathways below 10 Gy. The median follow up was 3 years. Tumor growth control was achieved in all cases. In GH-producing tumors, four of six cases evaluated were endocrinologically normalized (serum GH < 10 mIU /L, somatomedin C < 450 ng/ml), and the remaining two cases also showed a steady decrease in the GH and somatomedin level. In ACTH- producing tumors, three of six cases were endocrinologically normalized (24-hour urinary-free cortisol < 90 mg/day), two were unchanged, and one showed hormonal recurrence 3 years after radiosurgery. Notably, there were no cases of permanent hypopituitarism or visual symptoms caused by radiosurgery. CONCLUSIONS: The authors data indicate that GKS can be a safe salvage therapy for invading pituitary adenomas, with effectiveness equivalent to conventional radiation therapy but with less risk of causing radiation-induced injury to the surrounding structures.

53.

**Year:** 2000

**Patient number:** 163

**Author:** Vladyka, V.; Liscák, R.; Simonová, G.; Chytka, T.; Novotný, J., Jr.; Vymazal, J.; Marek, J.; Hána, V.; Vavros, D.

**Reference:** Casopis lékařů českých, 139, 24, 757-66, 2000

**Title:** Radiosurgical treatment of hypophyseal adenomas with the gamma knife: results in a group of 163 patients during a 5-year period

**Abstract:**BACKGROUND: Gamma knife radiosurgery of pituitary adenomas is considered to be very perspective. It can be a very useful complement of traditional microsurgery, pharmacotherapy or fractionated radiotherapy which are seldom a sufficient treatment on their own. The modern radiosurgery does not offer the experience representative enough in this indication. We can offer results of medium long follow-up for tumor growth and hormonal hypersecretion of pituitary adenomas in a relatively large series of patients. METHODS AND RESULTS: We have analyzed a group of 163 patients with pituitary adenoma treated with gamma knife during 5 years and followed 12-60 months, median 24 months after irradiation. An antiproliferative effect has been achieved in 1-2 years using the minimal dose to the margin 16-35 Gy, median 20 Gy in all our patients who were controlled by MRI (n = 126 patients). One half of these adenomas

evidently decreased their size. Our effective antiproliferative dose was safe for the surrounding structures. The hormonal normalization has been achieved at 50.4% from 133 hypersecreting adenomas (39/91 = 43% of acromegalics, 11/13 = 85% of patients with Cushing's disease, 2/9 = 22% of patients with Nelson's syndrome, 11/18 = 61% of prolactinomas). The median latency was 12 months. The minimal dose to the margin was 10-45 Gy, median 35 Gy. Rare side effects were provoked only by increasing the dose to influence the hypersecretion-the development of partial hypopituitarism in 3.1% of patients, the panhypopituitarism in 0.6% of patient and there was 1 hemianopic visual field defect (0.6%). **CONCLUSIONS:** Radiosurgery by gamma knife has a similar value for pituitary adenomas as microsurgery has with different distribution of advantages and drawbacks. This makes it suitable for the combined treatment where pharmacotherapy has its place under special conditions. Fractionated radiotherapy has now a marginal importance.

54.

**Year:** 2000

**Patient number:** 223

**Author:** Zhang, N.; Pan, L.; Dai, J.; Wang, B.; Wang, E.; Zhang, W.; Cai, P.

**Reference:** Stereotactic and functional neurosurgery, 75, 2-3, 123-8, 2000

**Title:** Gamma Knife radiosurgery as a primary surgical treatment for hypersecreting pituitary adenomas

**Abstract:**OBJECT: To estimate the efficacy of Gamma Knife radiosurgery (GKR) especially as a primary surgical treatment for hypersecreting pituitary adenomas. METHODS: 274 patients were treated with GKR. The mean tumor volume was 1.86 cm<sup>3</sup>. The mean peripheral dose was 28.7 Gy. RESULTS: 223 patients were followed up for an average of 31.6 months. The dose related to the tumor growth control and endocrinological normalization was detailed and statistical analysis of the data was performed. CONCLUSION: GKR as a primary surgical treatment for hypersecreting pituitary adenomas may be safe and effective. Copyright 2001 S. Karger AG, Basel.

55.

**Year:** 2000

**Patient number:** 79

**Author:** Zhang, N.; Pan, L.; Wang, E. M.; Dai, J. Z.; Wang, B. J.; Cai, P. W.

**Reference:** Journal of neurosurgery, 93, Suppl 3, 6-9, 2000

**Title:** Radiosurgery for growth hormone-producing pituitary adenomas

**Abstract:**OBJECT: The authors sought to evaluate the effect of gamma knife radiosurgery (GKS) on growth hormone (GH)-producing pituitary adenoma growth and endocrinological response. METHODS: From 1993 to 1997, 79 patients with GH-producing pituitary adenomas were treated with GKS. Seventy-six patients had acromegaly. Sixty-eight patients were treated with GKS as the primary procedure. The tumor margin was covered with a 50 to 90% isodose and the margin dose was 18 to 35

Gy (mean 31.3 Gy). The dose to the visual pathways was less than 10 Gy except in one case. Sixty-eight patients (86%) were followed for 6 to 52 months. Growth hormone levels declined with improvement in acromegaly in all cases in the first 6 months after GKS. Normalization of the hormone levels was achieved in 23 (40%) of 58 patients who had been followed for 12 months and in 96% of cases for more than 24 months (43 of 45), or more than 36 months (25 of 26), respectively. With the reduction of GH hormone levels, 12 of 21 patients with hyperglycemia regained a normal blood glucose level ( $p < 0.001$ ). The tumor shrank in 30 (52%) of 58 patients who had been followed for 12 months ( $p < 0.01$ ), 39 (87%) of 45 patients for more than 2 years ( $p = 0.02$ ), and 24 (92%) of 26 patients for more than 36 months. In the remainder of patients tumor growth ceased. **CONCLUSIONS:** Gamma knife radiosurgery for GH-producing adenomas showed promising results both in hormonal control and tumor shrinkage. A margin dose of more than 30 Gy would seem to be effective in improving the clinical status, reducing high blood glucose levels, and normalizing hypertension.

56.

**Year:** 1999

**Patient number:** 63

**Author:** Inoue, H. K.; Kohga, H.; Hirato, M.; Sasaki, T.; Ishihara, J.; Shibasaki, T.; Ohye, C.; Andou, Y.

**Reference:** Stereotactic and functional neurosurgery, 72, Suppl 1, 125-31, 1999

**Title:** Pituitary adenomas treated by microsurgery with or without Gamma Knife surgery: experience in 122 cases

**Abstract:** The clinical outcome of 122 patients with pituitary adenomas treated by microsurgery and/or Gamma Knife radiosurgery (GKRS) was analyzed to evaluate patient selection criteria and the role of GKRS. Sixty-six resections were performed in 59 patients. All tumors were macroadenomas, except for 5 ACTH-producing adenomas. Twenty-four of the 31 hypersecreting adenomas showed normal serum hormone values after treatment. Postoperative complications were rhinorrhea, cranial nerve palsies, and a small thalamic infarct. GKRS was performed on 18 of the operated patients because of residual tumors, mostly in the cavernous sinus. Thirty-five of the 63 patients treated by GKRS were followed for more than 2 years. All adenomas except 2 were stable or had decreased in size. Eleven of 17 functioning adenomas showed normal serum hormone values after treatment. It is concluded that tumors that compress the optic pathway should be removed and that residual tumors in the cavernous sinus are good indications for radiosurgery.

57.

**Year:** 1999

**Patient number:** 25

**Author:** Jokura, H.; Yoshimoto, T.

**Reference:** Japanese Journal of Neurosurgery, 8, 6, 403-412, 1999

**Title:** Value of gamma knife radiosurgery for tumors invading cavernous sinus

**Abstract:** The usefulness of radiosurgery for cavernous sinus tumors was evaluated based on our experience and recent published reports from other institutes. Twenty-six meningiomas involving the cavernous sinus were treated by radiosurgery. The length of follow-up averaged 3 years. Tumors regressed in 40% and remained stable in 56% of cases. A total of 96% of the tumors were controlled with only a few minor complications. We believe surgical resection to reduce the volume of the tumor without causing new neurological deficits, followed by radiosurgery on the tumor located in the cavernous sinus is the best choice in many cases. Twenty-five pituitary adenomas with cavernous sinus invasion were treated by a combination of trans-sphenoidal removal and radiosurgery. All the tumors are controlled in terms of volume during the follow-up (average of 34 months). There were no new neurological deficits, including visual disturbance. Hormone elevation was able to be corrected at an early stage without pituitary insufficiency more by radiosurgery than by fractionated radiation. However, to obtain good results by radiosurgery, it must be preceded by complete surgical decompression of optic nerves and chiasma from the tumor.

58.

**Year:** 1999

**Patient number:** 23

**Author:** Kim, M. S.; Lee, S. I.; Sim, J. H.

**Reference:** Stereotactic and functional neurosurgery, 72, Suppl 1, 119-24, 1999

**Title:** Gamma Knife radiosurgery for functioning pituitary microadenoma

**Abstract:** Transsphenoidal microsurgery remains the treatment of choice for pituitary microadenomas. One hundred and six patients were treated with Gamma Knife radiosurgery (GKRS) for pituitary adenomas, and of these, 23 patients (1 male, 22 female) had microadenomas. Twenty-two of these patients were followed up and endocrinological tests were available for 15 of these 22. Thirteen of these 15 had prolactinomas, while the remaining 2 had acromegaly. The follow-up period was from 3 to 26 months (median 12 months). The mean age was 33.6 years (range 21 to 60 years). The mean maximum tumor dose was 35.7 Gy and the mean margin dose was 22 Gy. Serum prolactin (PRL) was normalized in three patients, decreased in eight and unchanged in two. The growth hormone (GH) secretion in the acromegalic patients has remained unchanged through the follow-up period. Thus, GKRS is a valuable adjuvant to transsphenoidal microsurgery for patients with pituitary microadenomas.

59.

**Year:** 1999

**Patient number:** 37

**Author:** Kim, S. H.; Huh, R.; Chang, J. W.; Park, Y. G.; Chung, S. S.

**Reference:** Stereotactic and functional neurosurgery, 72, Suppl 1, 101-10, 1999

**Title:** Gamma Knife radiosurgery for functioning pituitary adenomas

**Abstract:** Stereotactic radiosurgery has been an important treatment modality in the treatment of pituitary adenomas. However, it has the disadvantage of a delayed effect on hormonal normalization compared with microsurgical resection of functioning pituitary adenomas. To define the efficacy of radiosurgery in the treatment of functioning pituitary adenomas, 37 cases with a mean follow-up duration of 26.9 months were analyzed. There were 18 prolactinomas, 11 cases with acromegaly, and 8 cases with Cushing's disease. The mean maximum dose was 54.8 Gy. The tumor margin was encompassed within the 50 to 90% isodose. The level of serum prolactin, growth hormone, and 24-hour urine free cortisol were evaluated for hormonal follow-up according to the relevant endocrinopathy. There was 35.1% hormonal normalization and an 81.8% decline in hormone levels to below 50% of the preoperative value (hormonal response). Hormonal normalization was obtained in 13 patients (mean latency = 22 months). A hormonal response was seen in 30 patients (mean latency = 7.6 months). The maximum dose and tumor volume included in the prescription isodose were significantly correlated with the latency period from radiosurgery to hormonal normalization. These results suggest that early hormonal normalization can best be achieved by a high maximum dose (at least 55 Gy) and broad coverage of the target tumor volume within the prescription dose thereby increasing the integral dose.

60.

**Year:** 1999

**Patient number:** 73

**Author:** Mokry, M.; Ramschak, Schwarzer S.; Simbrunner, J.; Ganz, J. C.; Pendl, G.

**Reference:** Stereotactic and Functional Neurosurgery, 72, SUPPL. 1, 88-100, 1999

**Title:** A six year experience with the postoperative radiosurgical management of pituitary adenomas

**Abstract:** Since April 1992, 73 consecutive patients with pituitary adenomas were treated with radiosurgery. There were 31 hormonally inactive adenomas and 42 hormonally active adenomas. All but three patients had been subjected to one or more surgical procedures prior to radiosurgery. Three patients had received fractionated radiotherapy. In the inactive adenoma group, the mean target volume was 4.4 plus-or-minus sign 3 cm<sup>3</sup> and the mean prescription dose was 13.8 plus-or-minus sign 1.5 Gy. In the prolactinoma patients, the mean target volume was 6.7 plus-or-minus sign 9 cm<sup>3</sup> and the mean prescription dose was 14.2 plus-or-minus sign 4 Gy. In the acromegalic patients, the mean target volume was 2.9 plus-or-minus sign 2.5 cm<sup>3</sup> and the mean prescription dose was 16 plus-or-minus sign 4 Gy. ACTH-secreting adenomas had a mean target volume of 3.6 plus-or-minus sign 5.5 cm<sup>3</sup> with a mean prescription dose of 17 plus-or-minus sign 4.8 Gy. The mean follow-up time was 28.9 plus-or-minus sign 21.5 months. Follow-up data was available in 83.6% of the patients. Tumor control was achieved in 98.3% and the endocrinological cure rate was 57%. Pituitary function deteriorated in 19.2%. No patient suffered from radiation induced visual damage. It would seem that postoperative radiosurgery for residual or recurrent pituitary adenomas may be a safe technique that can increase the frequency of therapeutic success.

61.

**Year:** 1998

**Patient number:** 37

**Author:** Ikeda, H.; Jokura, H.; Yoshimoto, T.

**Reference:** Radiation oncology investigations, 6, 1, 26-34, 1998

**Title:** Gamma knife radiosurgery for pituitary adenomas: usefulness of combined transsphenoidal and gamma knife radiosurgery for adenomas invading the cavernous sinus

**Abstract:** Thirty-seven of 317 patients with pituitary adenoma who underwent transsphenoidal operation from 1989 to 1996 received adjuvant gamma knife radiosurgery. Gamma knife surgery was performed mainly in patients with endocrinologically inactive tumor for tumor regrowth invading the cavernous sinus, and in patients with endocrinologically active tumor for incomplete removal invading the cavernous sinus. The maximum radiation dose was 25-60 Gy. The periphery of the tumor usually received 50% of the maximum dose. Thirteen patients were followed up for longer than 2 years (mean 45 months) after combined therapy. Magnetic resonance imaging (MRI) showed changes in signal intensity on both T1- and T2-weighted images as early as 3 months after radiotherapy. Serial MRI showed all 13 patients had achieved excellent response. Patients with endocrinologically active tumors showed normalized hormone levels 24 months after gamma knife surgery except for one patient with acromegaly. The basal value of pituitary hormones remained normal during the follow-up period, and four female patients became pregnant without hormonal therapy. Combined transsphenoidal surgery and gamma knife radiosurgery can preserve normal pituitary function and eradicate adenoma invading the cavernous sinus.

62.

**Year:** 1998

**Patient number:** 16

**Author:** Landolt, A. M.; Haller, D.; Lomax, N.; Scheib, S.; Schubiger, O.; Siegfried, J.; Wellis, G.

**Reference:** Journal of neurosurgery, 88, 6, 1002-8, 1998

**Title:** Stereotactic radiosurgery for recurrent surgically treated acromegaly: comparison with fractionated radiotherapy

**Abstract:** 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.

63.

**Year:** 1998

**Patient number:** 65

**Author:** Lim, Y. J.; Leem, W.; Kim, T. S.; Rhee, B. A.; Kim, G. K.

**Reference:** Stereotactic and Functional Neurosurgery, 70, SUPPL. 1, 95-109, 1998

**Title:** Four years' experience in the treatment of pituitary adenomas with gamma knife radiosurgery

**Abstract:** To determine the tumor control rates and endocrinological responses after stereotactic radiosurgery for pituitary adenomas, we reviewed our experience in 65 patients (40 men, 25 women) treated in the Gamma Knife during the last 4 years. The mean age was 41.6 years (range 19-69 years). 43 patients had endocrinologically active tumors (20 growth hormone-secreting, 19 prolactin-secreting and 4 ACTH-secreting adenomas). 22 had nonfunctioning adenomas. 39 patients had a macroadenoma and 26 patients had a microadenoma. 33 patients underwent Gamma Knife radiosurgery for recurrent or residual tumors after microsurgery. 50 patients have had follow-up neuroimaging studies and /or hormonal evaluation. The follow-up period was 25.5 months (range 3 to 54 months). The margin of the tumor was incorporated within the 50 to 90% isodose. The mean number of isocenters was 3.8 and the mean marginal dose was 25.4 Gy (range 15 to 36 Gy). 27 out of 40 patients (65.7%) showed decreased tumor volume to less than 50% of the initial volume. In 17 out of 38 patients (44.7%) with endocrinologically active tumors, the hormonal level fell to within the normal range. Two patients had delayed complications: in one case there was pituitary insufficiency and in the other a visual disturbance. Gamma Knife radiosurgery seems to be effective adjuvant therapy for pituitary adenoma in selected cases. More long-term follow-up is required to evaluate the efficacy and side effects further.

64.

**Year:** 1998

**Patient number:** 30

**Author:** Martinez, R.; Bravo, G.; Burzaco, J.; Rey, G.

**Reference:** Stereotactic and Functional Neurosurgery, 70, SUPPL. 1, 110-118, 1998

**Title:** Pituitary tumors and gamma knife surgery. Clinical experience with more than two years of follow-up

**Abstract:** 30 patients with Pituitary tumors were treated in our unit and followed for 26-45 months. 14 patients had nonsecreting adenomas, 7 had acromegaly, 5 had

prolactinomas, 3 had Cushing's disease. One patient had a choristoma of the pituitary stalk. The patient with a choristoma, 7 patients with nonsecreting adenomas, 4 with acromegaly, 1 prolactinoma and 3 with Cushing's disease had been operated by transsphenoidal microsurgery prior to Gamma Knife (GK) treatment. From this group, one patient with a nonsecreting adenoma and two with acromegaly had undergone fractional external radiotherapy after surgery. Stereotactic MRI localization had been used in all cases. All the tumors showed either a reduction in volume or cessation of growth; 85% of the patients with acromegaly showed normalization of growth hormone (GH) levels. Normalization of ACTH levels occurred in the 3 patients with Cushing's disease. All the patients with prolactinomas showed reduction of prolactin levels but normalization did not occur. However, in 3 cases the bromocriptine could be withdrawn. Deterioration of vision was not observed. One patient suffered transient paresis of the third cranial nerve that improved with steroids. Panhypopituitarism appeared in one case of Cushing's disease two years after the treatment. In the remaining cases there were no changes in their previous physiological pituitary function. We conclude that GK radiosurgery in pituitary tumors is an effective alternative to transsphenoidal microsurgery when compression of surrounding structures does not exist, and it can efficiently replace conventional irradiation.

65.

**Year:** 1998

**Patient number:** 25

**Author:** Morange, Ramos I.; Regis, J.; Dufour, H.; Andrieu, J. M.; Grisoli, F.; Jaquet, P.; Peragut, J. C.

**Reference:** Stereotactic and Functional Neurosurgery, 70, SUPPL. 1, 127-138, 1998

**Title:** Short-term endocrinological results after gamma knife surgery of pituitary adenomas

**Abstract:** We report our preliminary results after the radiosurgical treatment of 25 secreting pituitary adenomas with a mean follow-up of 20 months (range 6-36 months). Fifteen acromegalic patients showed a decrease of 65% in mean growth hormone (GH) levels after 6 months and of 77% after 12 months. Only 3 patients (20%) are considered to be in remission (mean GH and IGF1 level into the normal range). A decrease of prolactin (PRL) was noted in 46% and 64% at 6 and 12 months after radiosurgery in 4 patients with prolactinomas. There was no case of PRL normalization. At present 3/4 patients have individual PRL levels slightly above the normal range. A normalization of Urinary Free Cortisol (UFC) was noticed in 4/6 (66%) patients Cushing's disease within 6-12 months. Pituitary deficiency was noticed in this series in 4/25 patients (16%) who received subtotal or total pituitary irradiation for large postoperative remnants of secreting adenomas poorly defined on magnetic resonance imaging (MRI).

66.

**Year:** 1998

**Patient number:** 25

**Author:** Morange, Ramos I.; Regis, J.; Dufour, H.; Andrieu, J. M.; Grisoli, F.; Jaquet, P.; Peragut, J. C.

**Reference:** Acta neurochirurgica, 140, 5, 437-43, 1998

**Title:** Gamma-knife surgery for secreting pituitary adenomas

**Abstract:** We report our preliminary results concerning 25 patients with secreting pituitary adenomas treated with stereotactic radiosurgery after partial transsphenoidal surgery and followed over a 6-36 month-period. Among the 15 acromegalic patients, a decrease of 65% in mean GH levels was achieved after 6 months and of 77% at 12 months after radiosurgery. Presently, only 3 patients (20%) are considered as in remission (mean GH and IGF1 level into the normal range). A decrease of 46% and 64% was observed at 6 and 12 months after radiosurgery in 4 patients with prolactinomas although no normalization of PRL levels occurred. Presently, 3/4 patients have individual PRL level slightly above the normal range. A normalization of Urinary Free Cortisol (UFC) was noticed in 4/6 (66%) patients with Cushing's disease within 6-12 months. No pituitary deficiency was noticed in this series with the exception of 4/25 patients (16%) who received subtotal or total pituitary irradiation for post-operative remnants of secreting adenomas poorly defined on MRI. One woman, who had undergone previously a conventional irradiation and presenting with a cavernous sinus adenoma reaching the optic nerve, developed an optic neuropathy. A second woman, with a cavernous sinus remnant, presented a cranial nerve palsy (VI) after the irradiation. We can conclude that radiosurgery using the Cobalt-60 Gamma-unit is, at least, as effective as conventional radiotherapy in the control of pituitary hormone hypersecretion from postoperative adenomas remnants with less adverse effects.

67.

**Year:** 1998

**Patient number:** 73

**Author:** Pan, L.; Zhang, N.; Wang, E.; Wang, B.; Xu, W.

**Reference:** Stereotactic and Functional Neurosurgery, 70, SUPPL. 1, 119-126, 1998

**Title:** Pituitary adenomas: The effect of gamma knife radiosurgery on tumor growth and endocrinopathies

**Abstract:** Seventy-three patients have been treated with Gamma Knife radiosurgery (GKR) for pituitary adenomas. 12 had undergone surgery prior to GKR. Three had had previous radiation therapy. The prescription dose administered to the tumor margin ranged from 9 to 35 Gy 65 patients were followed up for an average of 29 months. A slight expansion of tumor volume occurred in 3 cases. Otherwise, the tumor volume remained unchanged or decreased in the remainder. Endocrine changes were present in all except 3 cases. GKR was followed by a speedy decrease in raised serum hormone levels in the case of both growth hormone (GH) and adrenocortico-tropic hormone (ACTH). In 3 patients there was some visual deterioration associated with a slight increase in tumor volume. In 2 cases, the tumors were removed surgically. Some preliminary conclusions may be drawn. The dose required to correct an endocrinopathy may be higher than that required for control of tumor growth. The recommended prescription dose for

endocrine-active adenomas may be more than 30 Gy. While clinical improvement may be noted in patients with raised serum prolactin levels (PRL), normalization of the endocrinopathy may be less readily achieved than in the case of raised GH and ACTH levels. Gamma Knife radiosurgery as a primary treatment of pituitary adenomas can be safe and effective.

68.

**Year:** 1997

**Patient number:** 21

**Author:** Park, Y. G.; Kim, E. Y.; Chang, J. W.; Chung, S. S.

**Reference:** Surgical neurology, 48, 5, 488-93, 1997

**Title:** Volume changes following gamma knife radiosurgery of intracranial tumors

**Abstract:**BACKGROUND: The primary goal of radiosurgery for brain tumors is the prevention of further growth. The purpose of this article is to evaluate temporal changes of tumor volume after Gamma Knife radiosurgery on intracranial tumors. METHOD: Some 137 patients with 148 intracranial tumors who were treated with Gamma Knife radiosurgery and underwent radiological follow-up were reviewed. The tumors with high radiosensitivities to conventional external radiation were excluded. RESULT: The median radiological follow-up period was 12 months (range 1.5-38 months). Volume decreased after radiosurgery in 15 of 45 meningiomas; 10 of 37 schwannomas; 6 of 21 pituitary adenomas; 4 of 15 benign gliomas, including both of 2 subependymal giant cell astrocytomas; and 2 of 8 malignant gliomas. Some 87% of meningiomas and 60% of schwannomas whose volume had decreased began to shrink within 12 months and after 12 months, respectively. Transitory increase in volume preceded shrinkage in 16.2% of schwannomas, 13.3% of benign gliomas, 4.8% of pituitary adenomas, and 2.2% of meningiomas. Marked shrinkage occurred in 17 of 19 metastatic tumors and in all 3 neurocytomas shortly after radiosurgery. Of eight malignant gliomas, five began to grow 2-14 months (median = 5 months) after radiosurgery. CONCLUSION: Several points should be considered carefully while following up on patients after radiosurgery: the possibility of transient volume increase, tumor-specific volume change patterns, and the tumor-specific goals of radiosurgery.

69.

**Year:** 1997

**Patient number:** 34

**Author:** Wang, Enmin Pan Li; Zhou, Liangfu; Wang, Binjiang; Qin, Zhiyong; Cai, Peiwu; Dai, Jiazhong

**Reference:** Acta Academiae Medicinae Shanghai, 24, 2, 115-118, 1997

**Title:** Gamma knife radiosurgery in the treatment of growth hormone-producing pituitary adenomas: Preliminary results

**Abstract:**Purpose: To assess the effects of gamma knife radiosurgery on growth hormone-producing pituitary adenomas with the magnetic resonance imaging

stereotactic localization. Methods: Between October 1993 and April 1995, thirty-four patients (25 males and 9 females) with growth hormone-producing pituitary adenomas and acromegaly, were treated with gamma knife radiosurgery. Eight patients were recurrent tumors after pituitary surgery and/or radiation therapy, and the rest 26 patients were initially treated by gamma knife after failing to respond to medical therapy. Of all patients, eight with hyperglycemia, five with hypertension. The maximum diameter of the tumors ranged from 6 to 25 mm, with mean 13 mm. The mean marginal dose administered to the patients with previous radiation therapy was 16 Gy (13.5 to 19.5 Gy). The marginal dose given to previous untreated or those who only underwent surgery were 20 to 35 Gy (mean 30 Gy). Results: Thirty one patients have been followed from 9 to 26 months (mean 16 months). The remission of the acromegaly was obtained in 26 patients, sixteen of them with significant improvement. Twenty patients attained reduction of GH level, 13 of them returned to normal. Three of eight patients with hyperglycemia resumed their normal blood glucose. Tumors reduced in volume in seventeen, almost disappeared in ten. The rest were at least cessation of growth. Conclusions: The preliminary results demonstrate that: (1) the patients only with increased GH level and acromegaly, when marginal dose given more than 25 Gy, attained control of tumors and endocrinopathy, and improvement of clinical status; (2) more than 30 Gy given to tumor margin appeared to be effective in improving clinical status of the patients with hyperglycemia, and reducing high blood glucose level and hypertension; (3) there was no pituitary insufficiency complicated during the follow-up period of time.

70.

**Year:** 1997

**Patient number:** 40

**Author:** Wowra, B.; Horstmann, G. A.; Cibis, R.; Czempiel, H.

**Reference:** Der Radiologe, 37, 12, 1003-15, 1997

**Title:** Profile of ambulatory radiosurgery with the gamma knife system 2: Report of clinical experiences

**Abstract:** Gamma Knife radiosurgery (GKRS) was applied in 500 consecutive treatments for 445 patients within 2 years. Indications were arterio-venous malformations (93 patients), schwannomas of cranial nerves (75 patients), meningiomas (79 patients; 73 of the tumors involving the skull base), pituitary adenomas (40 patients), craniopharyngiomas (13 cases), gliomas (13 cases), rare indications (12 cases), and brain metastases (126 patients). In arterio-venous malformations two complications were observed whereas two other patients underwent surgery due to intracranial hemorrhage in the latent period after GKRS. In all cases follow-up with MRI showed evidence of an active obliteration process. Out of 24 patients with a follow-up over 1 year, angiography revealed complete obliteration in 9 patients so far. A partial obliteration was evidenced by MRI in 15 cases. In benign tumors (meningiomas and vestibular schwannomas) tumor control rates of 88% and 89% were achieved, respectively. Treatment related side effects were mild and rare; no facial palsy occurred after primary Gamma Knife treatment. GKRS was particularly effective in inoperable skull base meningiomas. Cerebral metastases were controlled in 89.5% by a single Gamma Knife treatment. The mean survival period

was 11.8 months. In patients receiving a single Gamma Knife treatment the mean survival time was 9.1 months. For patients undergoing multiple (up to 5) sessions of GKRS (because of new tumors) the mean survival period was 17.2 months. MRI showed evidence of adverse radiation reactions in 10/124 patients (8.1%) which were symptomatic in 3 patients (0.8%). The results obtained in patients with cerebral metastases emphasize that GKRS alone is as effective as the combined treatment of these lesions by surgery and fractionated radiotherapy. Our results demonstrated an attractively high therapeutic gain factor of Gamma Knife treatment in key indications of radiosurgery.

71.

**Year:** 1996

**Patient number:** 30

**Author:** Motti, E. D.; Losa, M.; Pieralli, S.; Zecchinelli, A.; Longobardi, B.; Giugni, E.; Ventrella, L.

**Reference:** Metabolism: clinical and experimental, 45, 8 Suppl 1, 111-4, 1996

**Title:** Stereotactic radiosurgery of pituitary adenomas

**Abstract:** The first gamma knife (GK) treatment of a pituitary adenoma in 1967 was meant as an alternative to the primitive surgical approaches that prevailed at the time, with consequent unsatisfactory results. Surprisingly, pituitary adenomas still account for only 7.8% of the 27,000 cases treated in GK centers worldwide. Transnasosphenoidal surgery has greatly improved and surgeons are reluctant to give up a relatively safe and effective operative technique. Radiosurgery is not currently vying to be the primary method of surgery, but has a definite role following failed pituitary surgery and for tumors that extend into the cavernous sinus. Of 300 patients treated in our GK service, 30 had pituitary adenomas and most had undergone surgery. To date, we have not noted any side effects in the pituitary group. Published information is also reviewed and divided, where possible, into the pre-computed tomography (CT) era and the era of CT-magnetic resonance imaging (MRI). Growth hormone (GH)-secreting adenomas and prolactinomas tend to be larger and cannot be treated with the high doses successful against corticotropin (ACTH)-secreting tumors in Cushing's disease. Radiation fall-off is steep in GK radiosurgery, with the 20% isodose curve being only millimeters away from the point of maximal radiation. The effective dose has mostly been decided on the basis of maintaining safe levels at the sensitive perisellar neural structures. The safety of GK treatment (with no mortality and no permanent morbidity) is compared with other radiosurgical techniques. Good patient response owes much to the cumulative experience of GK pioneers and also to recent advances in images and computers that have enabled increasingly precise stereotaxic targeting and dose planning.

72.

**Year:** 1996

**Patient number:** 27

**Author:** Park, Y. G.; Chang, J. W.; Kim, E. Y.; Chung, S. S.

**Reference:** Yonsei medical journal, 37, 3, 165-73, 1996

**Title:** Gamma knife surgery in pituitary microadenomas

**Abstract:** The application of transsphenoidal microsurgery in the management of pituitary microadenoma, long regarded as effective surgical treatment, has had a relatively low mortality and morbidity rate. However early failure and late recurrence has been reported in no small numbers. It has been proposed that stereotactic radiosurgery is an alternative treatment modality. Recent advances in neuroimaging permits precise targeting in radiosurgery of microadenomas. Additionally, a prompt hormonal reduction after the treatment is important for the patients with hormonally active microadenomas. The authors performed Gamma Knife radiosurgery in 27 patients with pituitary adenomas and observed the hormonal changes after radiosurgery in 19 patients with functioning microadenomas (5 with Cushing's disease, 7 with acromegaly, and 7 with prolactinoma). The maximum dose administered ranged from 25 to 75 Gy. The margin of the tumor was encompassed within the 50 to 90% isodose volume. The endocrinological status was assessed pre- and post-operatively. We measured the serum growth hormone and prolactin level, as well as the 24-hour urinary free- cortisol level. Normalization of the hormonal level was achieved in 6 cases, the majority of them within 10 months. The other 6 cases showed marked reduction of hormonal levels (less than 50% of preoperative levels) with a strong possibility of hormonal remission at further follow-up. The remaining 6 were failures. The cure for one case is still pending. It took approximately 1 approximately 3 months after the radiosurgery before the reduction of hormonal secretion began to show up with some improvement of symptoms. When the GKS was successful, hormonal secretion seemed to return to normal within 10 months. Although further follow-up is necessary to evaluate the long- term tumor control rate and hormonal effect, these initial results indicate a potential therapeutic role of radiosurgery in controlling hormone hypersecretion in pituitary microadenomas. Gamma knife radiosurgery is very promising in managing pituitary microadenoma with complementary of the transsphenoidal surgery.

73.

**Year:** 1996

**Patient number:** 78

**Author:** Yin, Lian Hu Gao Hong Ju; Wang, Xue Qing

**Reference:** Zhongguo Zhongliu Linchuang, 23, 6, 386-389, 1996

**Title:** The experience of treating pituitary adenomas using gamma knife

**Abstract:** From October 1993 to April 1994, one hundred patients with pituitary adenomas were treated by Gamma knife in our hospital. 78 cases were followed up from 6 to 12 months, MR was reexamined in 49 cases, the level of the blood PRL was reexamined in 12 cases, the level of the blood GH was reexamined in 10 cases. The results showed that both the control rates of the patients' symptoms and the size of tumor were 100%. There was obvious difference between the levels of the blood PRL pre-and post treatment. So was the blood GH. We consider that the short-term results of the treatment by Gamma knife to pituitary adenomas were good. The treatment dose adaptability and indications

are discussed in this paper.

74.

**Year:** 1995

**Patient number:** 13

**Author:** Marek, J.; Malík, J.; Fendrych, P.

**Reference:** Casopis lékařů českých, 134, 17, 543-6, 1995

**Title:** Initial experience of an endocrinologist with the treatment of hypophyseal adenomas with the Leksell gamma knife

**Abstract:**BACKGROUND. Surgery of pituitary adenomas is not quite satisfactory so far and in some patients it is associated with a high risk. Conventional radiotherapy is only partly successful. Only few hospitals have experience with treatment of pituitary adenomas with Leksell's gamma knife. The objective of the presented paper is to give an account of the authors' own results of treatment of pituitary adenomas by irradiation with Leksell's gamma knife. METHODS AND RESULTS. The treated group comprised 13 patients (6 women, 7 men, 25-72 years old, median 44 years) with a pituitary adenoma. Hormonally active acromegaly was recorded in 9 patients, a prolactinoma in one female patient, a functional adenoma in 3 patients. Twelve patients had been operated already previously, 3 of them twice. For visualization of the pituitary magnetic resonance (NMR) was used on a Magnetom apparatus 1.5 Tesla, Siemens Co. before surgery and one year after surgery. As hormonal indicators the following were examined: growth hormone (GH) profile in the course of the day and during the thyrotropin releasing hormone test (TRH), insulin-like growth factor I (IGF I), the prolactin level, the thyrotropin level (TSH) during the thyrotropin releasing hormone test (TRH) test the thyroxine level (T4) and the triiodothyronine level (T3), the plasma concentration of adrenocorticotropin (ACTH), the cortisol level, plasma testosterone level and 17-beta estradiol level. Complete recovery was achieved only in one female patient with acromegaly 18 months after irradiation, and in one patient with a prolactinoma a partial decline of hormone levels was recorded without detectable changes in the size of the adenoma. Only one female patient developed hypopituitarism. No other complications were recorded. CONCLUSIONS. Stereotactic irradiation with Leksell's gamma knife is valuable for treatment of pituitary adenomas and it is well tolerated therapy. Its effect is manifested only after several months. Complications in the sense of hypopituitarism may occur.

75.

**Year:** 1995

**Patient number:** 38

**Author:** Simonová, G.; Novotná, J.; Novotná, J., Jr.; Vladyka, V.; Liscák, R.

**Reference:** Casopis lékařů českých, 134, 17, 547-54, 1995

**Title:** Fractionated stereotaxic radiotherapy with the Leksell gamma knife

**Abstract:**BACKGROUND. Stereotactic radiotherapy is treatment of a small or medium-sized intracranial focus, using a fractionated regime and the stereotactic method.

It is carried out usually on linear accelerators. The objective of the present investigation was to test the possibility of stereotactic radiotherapy using Leksell's gamma knife and Leksell's stereotactic frame. **METHODS AND RESULTS.** During the period between April 1993 and November 1994 38 patients (16 women and 22 men aged 15-72 years) were indicated for stereotactic radiotherapy. The patients had the following diagnoses: adenoma of the epipharynx (1), low-grade gliomas (10), ependymoma (1), germinoma (1), meningioma (2), solitary metastases into the CNS (19), pinealomas (3) and chordoma (1). The volume of the tumour varied from 740 mm<sup>3</sup> to 37,000 mm<sup>3</sup>. Stereotactic fractionated radiotherapy was carried out using a Leksell Gamma Knife, Electa Instrument AB, Sweden. For assessment of the total fractionated dose a linear quadratic model was used. Thus assessed value was further modified in relation to the volume and radiobiology of the tumour, critical structures surrounding the treated lesion and other factors. The total fractionated dose to the maximum varied from 20 Gy to 60 Gy and the total fractionated dose on the periphery of the tumour from 12 Gy to 30 Gy. With regard to the short time interval which has elapsed since treatment it is not yet possible to evaluate completely the achieved results; it will be possible to do so after a time interval of 1-5 years following the operation. The patients tolerated the 2-5 day fixation with a stereotactic Leksell frame very well and none of the patients developed complications. **CONCLUSIONS.** Fractionated stereotactic radiotherapy with Leksell's gamma knife, using Leksell's stereotactic frame, is a very accurate therapeutic method with a minimal radiation load of surrounding brain tissue. It requires a short hospitalization period and is associated with no or only minimal complications and improves the quality of patient's lives.

76.

**Year:** 1995

**Patient number:** 41

**Author:** Vladyka, V.; Liscák, R.; Subrt, O.; Simonová, G.; Novotná, J.

**Reference:** Casopis lékařů českých, 134, 17, 539-42, 1995

**Title:** Use of the radiosurgery knife in the treatment of hypophyseal adenomas

**Abstract:**BACKGROUND. Surgery of pituitary adenomas did not produce quite satisfactory results. Therefore radiosurgery using Leksell's gamma knife has become the most widely used method which-with the contribution of MRI-meets the most important demands of aimed irradiation: a sufficiently high dose of radiation of the tumour and minimal radiation load of functionally important surrounding structures. The objective of the investigation was to assemble experience with this therapeutic method. **METHODS AND RESULTS.** During the period between October 1992 and September 1994 a total of 41 patients were treated: 16 men, 12-66 years old, mean age 40.8 years; 25 women age 16-76 years, mean age 50.2 years. Female:male ratio 1.5 : 1. In 30 patients (73.2%) a microsurgical operation had preceded, in 5 (12.2%) conventional fractionated radiotherapy and in 11 patients (26.9%) primary radiosurgery. As far as the type of pituitary adenoma is concerned, it conditioned acromegaly in 30, Cushing's syndrome in 3 or Nelson's syndrome in 1, or a prolactinoma was involved (in 2 patients). In five instances the adenoma was hormonally inactive. Its localization was most frequently intrasellar (36), less frequently parasellar (5). The range of administered doses varied as

regards the maximum between 12.5 and 80 Gy, the average being 46.8 Gy, to the periphery of the adenoma a dose of 10-49 Gy was administered, on average 24.7 Gy using a 50-80% isodose. The time interval after treatment is relatively short for detailed analysis or evaluation. During current evaluation the authors did not observe in any of the patients progression of the disease, and in several patients diminution of the tumour was found. Karnofski's score seemed to improve. **CONCLUSIONS.** Radiosurgery, using Leksell's gamma knife, is after failure of conservative and microsurgical therapeutic possibilities suitable further treatment of pituitary adenoma. In indicated cases it may be the first choice. Postirradiation follow up indicates promising effects, for more detailed evaluation a several years' interval is necessary.

77.

**Year:** 1994

**Patient number:** 35

**Author:** Pollock, B. E.; Kondziolka, D.; Lunsford, L. D.; Flickinger, J. C.

**Reference:** Acta neurochirurgica. Supplement, 62, 33-8, 1994

**Title:** Stereotactic radiosurgery for pituitary adenomas: imaging, visual and endocrine results

**Abstract:** To determine the endocrine, ophthalmologic, and tumor growth control responses after stereotactic radiosurgery using the gamma unit, we reviewed our experience in 35 patients with pituitary adenomas. Twenty-four females and 11 males (mean age 47 years, range 9-81 years) had radiosurgery with average follow-up of 26 months (range 6-60 months). Most patients were refractory to surgical removal. Fifteen patients had Cushing's disease. Prior transsphenoidal resection was performed in 14 patients (6 had two prior operations), fractionated radiotherapy in 3, and adrenalectomy in 2. In 11 evaluable patients, the hormone response was normalized in 8, decreased in 2 and increased in 1. Five patients remained on cortisol suppression. Of 12 patients with imaging follow-up, 4 had decreased tumor size, 6 had no change, and 2 had an increase; these 2 patients underwent subsequent surgery. Ten patients had acromegaly, and 6 had undergone prior surgery. Of 8 evaluable patients, growth hormone secretion has normalized in 3, decreased in 3, and increased in 2. Six tumors decreased in size, and 2 were unchanged. One patient had repeat resection 21 months after radiosurgery and one patient underwent repeat radiosurgery. Ten patients had non-secreting adenomas; all 10 had prior operations (1-4 operations, 6 underwent frontal craniotomy) and 5 had undergone fractionated radiotherapy. Eight patients had panhypopituitarism prior to radiosurgery. Four tumors decreased in size and 6 were without change. (ABSTRACT TRUNCATED AT 250 WORDS).

78.

**Year:** 1993

**Patient number:** 15

**Author:** Ganz, J. C.; Backlund, E. O.; Thorsen, F. A.

**Reference:** Stereotactic and functional neurosurgery, 61, Suppl 1, 30-7, 1993

**Title:** The effects of Gamma Knife surgery of pituitary adenomas on tumor growth and endocrinopathies

**Abstract:** Fifteen patients were treated in the Gamma Knife Unit and followed for 18 months or longer. Four patients had Cushing's disease, 4 had acromegaly, 3 had Nelson's syndrome and 3 had prolactinomas. One patient had no endocrinopathy. One of the patients with acromegaly and 2 of those with prolactinomas had been operated prior to Gamma Knife treatment. Radiological tumor localization was not an insuperable problem in this series. The effect of Gamma Knife treatment on the anterior pituitary neoplasia, as such, was consistently successful. All the tumors which received 10 Gy or more to the edge showed either a reduction in volume or at least cessation of growth. On the other hand, the effect of the treatment was less consistent in respect to the endocrinopathies. These results are discussed in respect of dose and tumor size. It is suggested that the role of the Gamma Knife in the treatment of pituitary adenomas requires further clarification, based on prospective studies.

79.

**Year:** 1991

**Patient number:** 21

**Author:** Thorén, M.; Rähn, T.; Guo, W. Y.; Werner, S.

**Reference:** Neurosurgery, 29, 5, 663-8, 1991

**Title:** Stereotactic radiosurgery with the cobalt-60 gamma unit in the treatment of growth hormone-producing pituitary tumors

**Abstract:** Stereotactic radiosurgery on the pituitary given with the cobalt-60 gamma unit was used in the treatment of 21 patients with growth hormone (GH)-producing pituitary adenomas and acromegaly. All but one patient had locally invasive macroadenomas, and in the majority of cases, there was parasellar growth. Radiosurgery was the initial treatment for seven patients. Fourteen patients were previously treated by pituitary surgery, eight of whom had undergone conventional external pituitary irradiation as well. All patients had clinical signs of active acromegaly before radiosurgery. The radiation doses given to the previously untreated patients or those who only underwent surgery were 40 to 70 Gy in each of one to three irradiations. The patients with previous external irradiation received a lower dose of 30 to 50 Gy in each of one or two irradiations. The patients were observed during a period of 1 to 21 years from the first radiosurgical session. Two young patients had a clinical remission with a substantial decline of GH levels to near normal serum profiles. Another eight patients obtained reduction of GH levels and clinical activity. More than half of the patients (11 of 21) had minor or no effects from the treatment. There were no complications from the radiosurgery except the development of pituitary insufficiency in 2 of 13 patients who did not undergo previous conventional external irradiation. The remission rates were lower than the results previously reported by us for radiosurgery for Cushing's disease. This may be a result of the predominance in the present study of invasive macroadenomas and single treatments and to the lower radiation doses used in the patients who underwent conventional irradiation previously. (ABSTRACT TRUNCATED AT 250 WORDS).

80.

**Year:** 1986

**Patient number:** 35

**Author:** Degerblad, M.; Rähn, T.; Bergstrand, G.; Thorén, M.

**Reference:** Acta endocrinologica, 112, 3, 310-4, 1986

**Title:** Long-term results of stereotactic radiosurgery to the pituitary gland in Cushing's disease

**Abstract:** Gamma radiation from  $^{60}\text{Co}$  delivered with stereotactic technique was given to the pituitary gland in 35 patients, aged 18-65 years, with Cushing's disease. The doses were 70-100 Gy in each single irradiation. The size of the sella turcica was normal in the majority of the patients. The observation time was 3-9 years in 29 patients. Out of them, 14 (48%) obtained clinical remission and normal urinary cortisol after one irradiation. Eight achieved remission after two to four irradiations. In total, 22 out of 29 patients (76%) obtained remission. In 12 of them remission was obtained in 1 year and in another 10 within 3 years. No recurrences were observed. Improvement was seen in 2 patients after one and three irradiations. Bilateral adrenalectomy was performed in 5 patients owing to unsatisfactory effect of irradiation. Pituitary insufficiency with gonadotropin, thyrotropin or corticotropin failure was demonstrated in 12 of 22 patients in remission. This occurred 4 months to 7 years after the first irradiation. Another 6 patients were followed less than 3 years after the first irradiation. Two obtained remission after the first treatment, whereas the other 4 improved. Stereotactic pituitary irradiation is suggested as a non-invasive therapeutic alternative in Cushing's disease for example in patients with considerable surgical risk or as a supplement to pituitary microsurgery.

81.

**Year:** 1982

**Patient number:** 20

**Author:** Thoren; Rahn; Hall; Backund

**Reference:** Dept. Endocrinology, Karolinska Hosp., 104 01 Stockholm, Sweden. English. (Cobalt-Radioisotopes). NOTNLM. 19820201., 1982

**Title:** STEREOTACTIC RADIOSURGERY AS TREATMENT IN PITUITARY-DEPENDENT CUSHING'S SYNDROME

**Abstract:** Twenty patients, 16 with pituitary-dependent Cushing's syndrome (CS) and 4 with Nelson's syndrome (NS), were treated with stereotactically- directed gamma radiation from  $^{60}\text{Co}$ . Ten of the 16 CS patients and 4/4

82.

**Year:** 1981

**Patient number:** 23

**Author:** Thoren, M.; Hall, K.; Rahn, T.

**Reference:** Acta Endocrinologica, 97, 1, 12-17, 1981

**Title:** SOMATOMEDIN A LEVELS IN PATIENTS WITH CUSHINGS DISEASE

**Abstract:** The serum levels of immunoreactive somatomedin A (SMA) in 23 patients with Cushing's disease, aged 6-61 yr, were within the range of healthy subjects for their ages. No correlation was found between SMA and the excretion of cortisol. After i.m. administration of hGH (human growth hormone) (8 IU = 4 mg) daily for 3 days there was a significant rise in SMA, both determined by radioimmunoassay and radioreceptor assay. Thus, no impairment was found in the GH-dependent SMA levels or the ability of hGH to generate somatomedin; the growth retarding effect of cortisol is most likely due to a direct effect on the tissue. After treatment with stereotactic radiation to the hypophysis there was a significant decrease in cortisol excretion without any change in SMA levels, indicating the possibility to achieve a selective impairment of the ACTH-cortisol axis.

83.

**Year:** 1980

**Patient number:** 17

**Author:** Rahn; Thoren; Hall; Backlund

**Reference:** Dept. Neurosurgery and Endocrinology, Karolinska sjukhuset, S-104 01 Stockholm, Sweden. English. NOTNLM. 19801201., 1980

**Title:** STEREOTACTIC RADIOSURGERY IN THE TREATMENT OF MB CUSHING

**Abstract:** Seventeen patients (14 women, 3 men) who had a pituitary-dependent Cushing syndrome were subjected to stereotactic radiosurgery. The immediate and follow-up results of this treatment are discussed. It was concluded that stereotactic radiosurgery is a therapeutic alternative to open selective adenectomy. (15 Refs).

84.

**Year:** 1980

**Patient number:** 18

**Author:** Rahn, T.; Thorén, M.; Hall, K.; Backlund, E. O.

**Reference:** Surgical neurology, 14, 2, 85-92, 1980

**Title:** Stereotactic radiosurgery in Cushing's syndrome: acute radiation effects

**Abstract:** Stereotactic radiosurgery was used for selective destruction of adrenocorticotrophic hormone (ACTH)-producing adenomas in 18 patients with Cushing's syndrome. A radiation-induced lesion in the most anterior part of the sella turcica caused remission of the disease. The acute increase in ACTH and cortisol secretion that occurred in the majority of patients had no predictable relationship to the final outcome. Decreased cortisol excretion during the first three weeks after treatment was positively correlated to favourable long-term results. The treatment is a therapeutic alternative to open selective excision of the adenoma.