



Gamma Knife® Radiosurgery



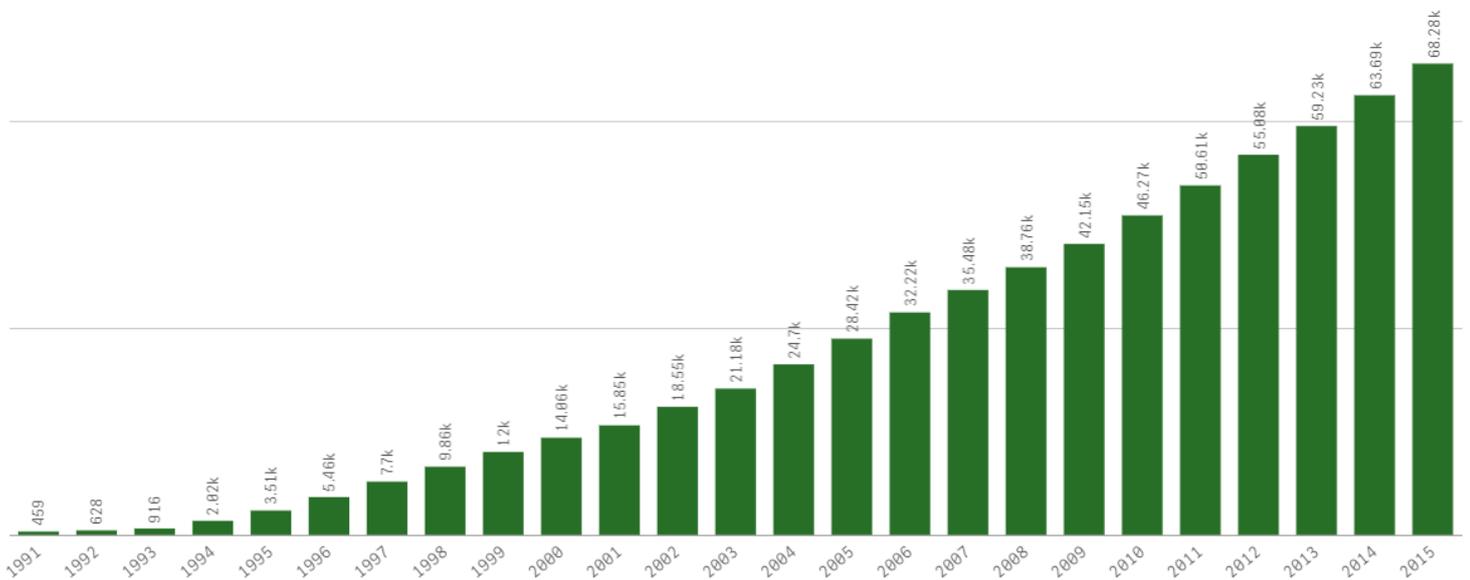
Pituitary Tumors Bibliography
1978 - November, 2016

PITUITARY TUMORS

Includes Gamma Knife-focused abstracts posted to PubMed during 1978 to November, 2016.

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Pituitary Tumors, cumulative patients treated with Leksell Gamma Knife® worldwide
1991 reflects cumulative numbers. 68-100% centers reporting

Secreting

Clinical Neurology and Neurosurgery.2016;145(8-13).Epub 2016/04/10

Microneurosurgery and subsequent gamma knife radiosurgery for functioning pituitary macroadenomas or giant adenomas: One institution's experience

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OBJECTIVE: Functioning pituitary macroadenoma and giant adenoma have large growth volumes and endocrinological abnormalities, requiring proper medical intervention. In this retrospective study, microneurosurgery and subsequent gamma knife radiosurgery (GKRS) is assessed for efficacy and safety for the treatment of functioning pituitary macroadenoma and giant adenoma. **METHODS:** Between January 2007 and December 2011, 59 patients with functioning pituitary macroadenoma (n=38) or giant adenoma (n=21) received microneurosurgical resection, and after three months, GKRS with average maximum radiation dose approximately 42Gy (range 30-66.7Gy). The median follow-up time was 54.3 months (range 36-85 months). **RESULTS:** The combined treatment controlled tumor growth in 81.4% (48/59) of patients, and improved the endocrinological status in 64.4% (38/59). Complications included hypopituitarism and visual deterioration (22 and 7 patients, respectively). Large tumor size at presentation was a risk factor for tumor recurrence, but not age, gender, invasion, radiosurgical dose, pituitary hormone status or follow-up period. Better outcomes were achieved by patients with macroadenoma than giant adenoma. **CONCLUSIONS:** Combined microneurosurgery and GKRS are safe and effective for functioning pituitary macroadenomas or giant adenomas. Tumor control and endocrinological improvement were satisfactory, with minimal complications.

Hormones (Athens).2016;15(1):122-8.Epub 2016/01/07

TSH-secreting pituitary adenomas treated by gamma knife radiosurgery: our case experience and a review of the literature

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A 43-year-old woman, previously misdiagnosed as having primary hyperthyroidism and treated with antithyroid drugs, presented to us with overt hyperthyroidism, high levels of thyroid hormones and elevated thyroid-stimulating hormone (TSH). Magnetic resonance imaging (MRI) revealed a pituitary microadenoma extending suprasellarly. The patient responded favorably to initial treatment with somatostatin analogs for 2 years but due to the escape phenomenon, TSH levels escalated and hyperthyroidism relapsed. Transsphenoidal adenectomy was applied but recurrence was again observed due to incomplete tumor removal. Gamma knife radiosurgery was finally employed 5.5 years ago, resulting in complete disease remission without evidence of long-term complications to date. Thyrotropin-secreting adenomas (TSHomas) are rare with an estimated prevalence of about one case per million. We retrieved from the literature 14 cases of TSHomas treated by gamma knife radiosurgery and compared the outcomes. Our results demonstrate the efficacy and safety of gamma knife radiosurgery for achieving remission in most of the cases, suggesting validation of this technique as an effective treatment option for the management of recurrent TSHomas.

Clinical Endocrinology.2016;84(4):524-31.Epub 2015/09/06

Gamma knife radiosurgery in patients with persistent acromegaly or Cushing's disease: long-term risk of hypopituitarism

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INTRODUCTION: For patient with a recurrent or residual acromegaly or Cushing's disease (CD) after resection, gamma knife radiosurgery (GKRS) is often used. Hypopituitarism is the most common adverse effect after GKRS treatment. The paucity of studies with long-term follow-up has hampered understanding of the latent risks of hypopituitarism in patients with acromegaly or CD. We report the long-term risks of hypopituitarism for patients

treated with GKRS for acromegaly or CD. **METHODS:** From a prospectively created, IRB-approved database, we identified all patients with acromegaly or CD treated with GKRS at the University of Virginia from 1989 to 2008. Only patients with a minimum endocrine follow-up of 60 months were included. The median follow-up is 159.5 months (60.1-278). Thorough radiological and endocrine assessments were performed immediately before GKRS and at regular follow-up intervals. New onset of hypopituitarism was defined as pituitary hormone deficits after GKRS requiring corresponding hormone replacement. **RESULTS:** Sixty patients with either acromegaly or CD were included. Median tumour volume at time of GKRS was 1.3 cm³ (0.3-13.4), and median margin dose was 25 Gy (6-30). GKRS-induced new pituitary deficiency occurred in 58.3% (n = 35) of patients. Growth hormone deficiency was most common (28.3%, n = 17). The actuarial overall rates of hypopituitarism at 3, 5 and 10 years were 10%, 21.7% and 53.3%, respectively. The median time to hypopituitarism was 61 months after GKRS (range, 12-160). Cavernous sinus invasion of the tumour was found to correlate with the occurrence of a new or progressive hypopituitarism after GKRS (P = 0.018). **CONCLUSIONS:** Delayed hypopituitarism increases as a function of time after radiosurgery. Hormone axes appear to vary in terms of radiosensitivity. Patients with adenoma in the cavernous sinus are more prone to develop loss of pituitary function after GKRS.

Neurosurgery. 2014 Sep;75(3):227-37; discussion 237.

Whole-sellar stereotactic radiosurgery for functioning pituitary adenomas.

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BACKGROUND:

Functioning pituitary adenomas (FPAs) can be difficult to delineate on postoperative magnetic resonance imaging, making them difficult targets for stereotactic radiosurgery (SRS). In such cases, radiation delivery to the entire sella has been utilized as a radiosurgical equivalent of a total hypophysectomy.

OBJECTIVE:

To evaluate the outcomes of a cohort of patients with FPA who underwent SRS to the whole-sellar region.

METHODS:

This is a retrospective review of patients who underwent whole-sellar SRS for FPA between 1989 and 2012. Sixty-four patients met the inclusion criteria: they were treated with whole-sellar SRS following surgical resection for persistently elevated hormone levels, and (1) no visible lesions on imaging studies and/or (2) tumor infiltration of dura or adjacent venous sinuses observed at the time of a prior resection. The median radiosurgical volume covering sellar structures was 3.2 mL, with a median margin dose of 25 Gy.

RESULTS:

The median endocrine follow-up was 41 months; 22 (68.8%) patients with acromegaly, 20 (71.4%) patients with Cushing disease, and 2 (50.0%) patients with prolactinoma achieved endocrine remission. The 2-, 4-, and 6-year actuarial remission rates were 54%, 78%, and 87%, respectively. New-onset neurological deficit was found in 4 (6.3%) patients following treatment. New-onset hypopituitarism was observed in 27 (43.5%) patients, with panhypopituitarism in 2 (3.2%). Higher margin/maximum dose were significantly associated with a higher remission rate and development of post-SRS hypopituitarism.

CONCLUSION:

Whole-sellar SRS for invasive or imaging-negative FPA following failed resection can offer reasonable rates of endocrine remission. Hypopituitarism following whole-sellar SRS is the most common complication.

World Neurosurg. 2014 Jul-Aug;82(1-2):195-201. doi: 10.1016/j.wneu.2013.01.127. Epub 2013 Feb 4.

Efficacy and safety of higher dose stereotactic radiosurgery for functional pituitary adenomas: a preliminary report.

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OBJECTIVE:

Single fraction stereotactic radiosurgery (SRS) is a common adjuvant therapy for hormonally active pituitary adenomas when surgical resection fails to control tumor growth or normalize hypersecretory activity. Marginal doses of 20-24 Gy are used at many centers and here we report our outcome data in patients treated with a higher marginal dose of 35 Gy.

METHODS:

Thirty-one patients with secretory pituitary adenomas (adrenocorticotropic hormone, n = 15; growth hormone, n = 13; prolactin, n = 2; thyroid-stimulating hormone, n = 1) were treated with 35 Gy to the 50% isodose line, and had a mean follow-up time of 40.2 months (range = 12-96). All patients were evaluated post-SRS for time to hormonal normalization, time to relapse, as well as incidence and time course of radiation-induced hypopituitarism and cranial neuropathies.

RESULTS:

Initial normalization of hypersecretion was achieved in 22 patients (70%) with a median time to remission of 17.7 months. After initial hormonal remission, 7 patients (32%) experienced an endocrine relapse, with a mean time to relapse of 21 months. New endocrine deficiency within any of the five major hormonal axes occurred in 10 patients (32%). One patient (3%) developed new-onset unilateral optic nerve pallor within the temporal field 3 years after SRS. Three patients (10%) reported transient new or increasing frontal headaches of unclear etiology following their procedures.

CONCLUSION:

Time to endocrine remission was more rapid in patients treated with 35 Gy, as compared to previously reported literature using marginal doses of 20-24 Gy. Rates of endocrine remission and relapse, post-SRS hypopituitarism, and radiation-induced sequelae were not increased following higher dose treatment.

World Neurosurg. 2014 Jul-Aug;82(1-2):e75-6. doi: 10.1016/j.wneu.2013.02.080. Epub 2013 Feb 28.

Stereotactic radiosurgery for functioning pituitary adenomas--a higher dose is better but only up to a point.

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KEYWORDS:

35 Gy; Gamma knife surgery; Optic apparatus; Optic nerves; Pituitary adenoma; Stereotactic radiosurgery

Comment on

Efficacy and safety of higher dose stereotactic radiosurgery for functional pituitary adenomas: a preliminary report. [World Neurosurg. 2014]

World Neurosurg. 2014 Jul-Aug;82(1-2):58-9. doi: 10.1016/j.wneu.2013.03.015. Epub 2013 Mar 14.

Stereotactic radiosurgery for functioning pituitary adenomas.

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KEYWORDS:

35 Gy; Gamma-knife surgery; Optic apparatus; Optic nerves; Pituitary adenoma; Stereotactic radiosurgery

Comment on

Efficacy and safety of higher dose stereotactic radiosurgery for functional pituitary adenomas: a preliminary report. [World Neurosurg. 2014]

J Clin Neurosci. 2013 Aug;20(8):1152-4. doi: 10.1016/j.jocn.2012.09.032. Epub 2013 Apr 12.

Undifferentiated sarcoma of the cavernous sinus after γ knife radiosurgery for pituitary adenoma.

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We report a rare case of gamma knife radiation-induced undifferentiated sarcoma in the cavernous sinus. A 24-year-old woman underwent resection of a growth hormone-secreting pituitary adenoma and gamma knife radiosurgery (maximal dose 24 Gray (Gy); marginal dose 16 Gy) for residual adenoma in the right cavernous sinus. Follow-up MRI showed the disappearance of the adenoma. Fifteen years later, she developed right oculomotor nerve palsy. MRI revealed a new tumor in the right cavernous sinus. Partial removal of the tumor was performed via a transsphenoidal approach. Histological diagnosis revealed undifferentiated sarcoma. The patient received three cycles of chemotherapy containing doxorubicin and ifosfamide, then carbon ion radiotherapy (65 GyE in

26 fractions). Subsequent MRI showed tumor regression for five months. To our knowledge, this is the first report of undifferentiated sarcoma following gamma knife radiosurgery for pituitary adenoma. As patients undergoing radiosurgery face the possibility of such neoplasms developing, long-term follow-up is required.

J Clin Neurosci. 2012 Jun;19(6):900-2. doi: 10.1016/j.jocn.2011.09.016. Epub 2012 Feb 19.

Delayed cerebrospinal fluid rhinorrhea after gamma knife surgery in a patient with a growth hormone-secreting adenoma.

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We report a patient who developed delayed cerebrospinal fluid (CSF) rhinorrhea 11 years after gamma knife radiosurgery for a growth hormone (GH)-secreting adenoma. The treatment dose was 18 Gy for the tumor margin (50% isodose). One year later, an MRI of the head revealed that the tumor size had decreased. Eleven years later, the patient developed CSF rhinorrhea from the left nostril. Subsequent MRI examination revealed complete remission of the tumor in the sella turcica and the empty sella. The patient was admitted for direct endoscopic surgical repair of the skull base. We suggest that the cause of the CSF rhinorrhea is secondary empty sella. The other potential causes may be the original invasiveness of the tumor or delayed radiation damage to the mucous membranes of the skull. Long-term follow-up is required to monitor recurrence of CSF rhinorrhea.

Acta Neurochir (Wien). 2012 Apr;154(4):665-6.

Single low dose adjuvant y knife radiosurgery for thyrotropin secreting pituitary adenoma.

Kasliwal MK, Gupta A, Sharma MS.

J Clin Neurosci. 2010 Mar;17(3):299-304. doi: 10.1016/j.jocn.2009.05.040. Epub 2010 Jan 13.

Gamma knife radiosurgery for growth hormone-producing adenomas.

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We evaluated the endocrinological outcomes of gamma knife radiosurgery (GKS) for the treatment of growth hormone (GH)-producing pituitary adenomas. Twenty-six patients treated with GKS (median treatment [tumour] volume: 0.8 mL; median marginal radiation dose: 20Gy) were followed for a median of 84 months. "Disease remission" was defined as either nadir levels of GH <1 microg/L during an oral glucose load, or random GH levels <2 microg/L and normal age-adjusted and sex-adjusted levels of insulin-like growth factor without pituitary suppressive medications. The remission rate was 38% (10/26) and the 5-year and 10-year actuarial remission rates were 16.9% and 47.4%, respectively. Two patients (8%) suffered hypopituitarism requiring medication, but no other serious deficits were observed. Although GKS requires a relatively long time to achieve hormonal remission, it is a very useful, long-term treatment for GH-producing adenomas. We propose that compared to continuing life-long medication, GKS is less invasive and more cost effective.

J Clin Endocrinol Metab. 2009 Sep;94(9):3400-7. doi: 10.1210/jc.2008-2772. Epub 2009 Jun 9.

Long-term results of stereotactic radiosurgery in secretory pituitary adenomas.

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CONTEXT:

To date, no study reported long-term follow-up results of gamma knife stereotactic radiosurgery (SR).

OBJECTIVE:

The aim of the study was to determine long-term efficacy and adverse effects of SR in secreting pituitary adenomas.

DESIGN:

We conducted a retrospective study of patients treated by SR in the center of Marseille, France, with a follow-up of at least 60 months.

PATIENTS:

A total of 76 patients were treated by SR for acromegaly (n = 43), Cushing's disease (CD; n = 18), or prolactinoma (n = 15) as a primary (n = 27) or adjunctive postsurgical treatment (n = 49).

MAIN OUTCOME MEASURES:

After withdrawal of antiseecretory drugs, patients were considered in remission if they had mean GH levels below 2 ng/ml and normal IGF-I (acromegaly), normal 24-h urinary free cortisol, and cortisol less than 50 nmol/liter after low-dose dexamethasone test (CD) or two consecutive normal samplings of prolactin levels (prolactinoma).
RESULTS:

After a mean follow-up of 96 months, 44.7% of the patients were in remission. Mean time to remission was 42.6 months. Twelve patients presented late remission at least 48 months after SR. Two patients with CD presented late recurrence 72 and 96 months after SR. Forty percent of patients treated primarily with SR were in remission. Target volume and initial hormone levels were significant predictive factors of remission in univariate analysis. Radiation-induced hypopituitarism was observed in 23% patients; in half of them, hypopituitarism was observed after a mean time of 48 to 96 months. Twenty-four patients were followed for more than 120 months; rates of remission and hypopituitarism were similar to the whole cohort.

CONCLUSIONS:

SR is an effective and safe primary or adjunctive treatment in selected patients with secreting pituitary adenomas.

Stereotact Funct Neurosurg. 2008;86(5):292-6. doi: 10.1159/000151717. Epub 2008 Aug 30.

Endocrine response after gamma knife-based stereotactic radiosurgery for secretory pituitary adenoma.

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PURPOSE:

To examine treatment outcomes of Gamma Knife-based stereotactic radiosurgery (GK-based SRS) for secretory pituitary adenomas.

MATERIALS AND METHODS:

25 patients were treated with GK-based SRS for secretory pituitary adenomas with ≥ 12 months of follow-up.

RESULTS:

For prolactinomas, 2 of 4 patients (50%) showed normalization of serum prolactin at a mean time of 18 months. One of 4 had a $\geq 50\%$ decrease but still abnormal prolactin levels. For adrenocorticotrophic hormone-secreting tumors, 6 of 12 patients (50%) showed normalization of their endocrine levels at a median of 10 months. An additional 2 (17%) had a $\geq 50\%$ decrease. For growth hormone-secreting tumors, 4 of 9 patients (44%) showed normalization of endocrine levels at a median time of 30 months. Two patients (22%) had $\geq 50\%$ lower but abnormal endocrine levels.

CONCLUSION:

GK-based SRS provides a reasonable rate of endocrine normalization of secretory pituitary adenoma. The time to endocrine response is shorter than reported for fractionated external beam radiotherapy. There is a low risk of optic neuropathy.

Neurosurgery. 2008 Jun;62(6):1271-6; discussion 1276-8. doi: 10.1227/01.neu.0000333298.49436.0e.

Pituitary tumor type affects the chance of biochemical remission after radiosurgery of hormone-secreting pituitary adenomas.

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OBJECTIVE:

Reported biochemical remission rates have ranged widely after stereotactic radiosurgery for patients with hormone-secreting pituitary adenomas. Confounding variables include histology, radiation dose, use of pituitary-suppressive medications, and length of follow-up.

METHODS:

A retrospective review of 46 patients with pituitary adenomas (growth hormone-secreting, n = 27; prolactin-secreting, n = 11; adrenocorticotropin-secreting, n = 8) undergoing radiosurgery between January 1990 and December 2003 was conducted. All received a tumor margin dose of 18 Gy or more and were off pituitary-suppressive medications for at least 1 month before radiosurgery. The groups were similar with regard to irradiated volume, radiation dose, and follow-up. The median endocrinological follow-up after radiosurgery was 54 months.

RESULTS:

The 4-year remission rates were 87% for patients with Cushing's disease, 67% for patients with acromegaly, and 18% for patients with prolactinomas. Patients with oversecretion of adrenocorticotropin or growth hormone

were more likely to achieve remission after radiosurgery than patients with prolactinomas (hazard ratio, 4.4; 95% confidence interval, 1.1-18.2; P = 0.04). Of 44 patients with normal or partial anterior pituitary function before radiosurgery, 16 (36%) developed one or more new anterior pituitary deficits. The incidence of new anterior pituitary deficits was 26% at 4 years. No differences were noted in the incidence of new anterior deficits among the groups.

CONCLUSION:

There seems to be a differential sensitivity after radiosurgery for hormone-secreting pituitary adenomas. Remission rates are greater for patients with Cushing's disease and acromegaly, whereas radiosurgery is less effective in achieving biochemical remission for patients with prolactinomas.

J Neurosurg. 2007 Jun;106(6):988-93.

Gamma Knife surgery for adrenocorticotrophic hormone-producing pituitary adenomas after bilateral adrenalectomy.

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OBJECT:

Patients with adrenocorticotrophic hormone (ACTH)-secreting pituitary adenomas may require a bilateral adrenalectomy to treat their Cushing's disease. Approximately one third of these patients, however, will experience progressive enlargement of the residual pituitary adenoma, develop hyperpigmentation, and have an elevated level of serum ACTH. These patients with Nelson's syndrome can be treated with Gamma Knife surgery (GKS).

METHODS:

The prospectively collected University of Virginia Gamma Knife database of patients with pituitary adenomas was reviewed to identify all individuals with Nelson's syndrome who were treated with GKS. Twenty-three patients with a minimum of 6 months of follow up were identified in the database. These patients were assessed for tumor control (that is, lack of tumor growth over time) with neuroimaging studies (median follow-up duration 22 months) and for biochemical normalization of their ACTH levels (median follow-up duration 50 months). Neuroimaging follow-up studies were available for 22 patients, and endocrine follow up was available for 15 patients in whom elevation of ACTH levels was documented prior to GKS. In the 22 patients in whom neuroimaging follow-up studies were available, 12 had a decrease in tumor size, eight had no tumor growth, and two had an increase in tumor volume. Ten of 15 patients with elevated ACTH levels prior to GKS showed a decrease in their ACTH levels at last follow up; three of these 10 patients achieved normal ACTH levels (< 50 pg/ml) and the other five patients with initially elevated values had an increase in ACTH levels. Ten patients were thoroughly evaluated for post-GKS pituitary function; four were found to have new pituitary hormone deficiency and six did not have hypopituitarism after GKS. One patient suffered a permanent third cranial nerve palsy and four patients are now deceased.

CONCLUSIONS:

Gamma Knife surgery may control the residual pituitary adenoma and decrease ACTH levels in patients with Nelson's syndrome. Delayed hypopituitarism or cranial nerve palsies can occur after GKS. Patients with Nelson's syndrome require continued multidisciplinary follow-up care. Given the difficulties associated with management of Nelson's syndrome, even the modest results of GKS may be helpful for a number of patients.

Zhonghua Wai Ke Za Zhi. 2006 Mar 15;44(6):416-9.

[Gamma knife for hypersecreting pituitary adenoma: analysis of 120 cases].

[Article in Chinese]

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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 data 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.

Acta Neurochir (Wien). 2006 Aug;148(8):903-8; discussion 908. Epub 2006 Jun 19.

Transient MR changes and symptomatic epilepsy following gamma knife treatment of a residual GH-secreting pituitary adenoma in the cavernous sinus.

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OBJECTIVE:

To report a rare side effect of gamma knife treatment of pituitary macroadenoma.

CASE REPORT:

In a forty-one-year old female patient acromegaly was diagnosed due to a growth hormone secreting pituitary macroadenoma. Following transsphenoidal surgery the patient underwent gamma knife treatment for persistent uncontrolled acromegaly activity of residual tumor, infiltrating the left cavernous sinus. 15 months later, complex partial seizures were diagnosed and 17 months after gamma knife treatment a gadolinium enhancing lesion was detected in her left medial temporal lobe. Radiation induced changes, radiation necrosis or a glioma were considered. Neuropsychological testing indicated potentially significant post-surgical deficits. Therefore, surgical action was postponed and anti-epileptic treatment was started. Four months later she was free of seizures and an MR scan showed an almost complete regression of the gadolinium enhancing lesion, indicating that it had been due to radiation induced changes.

CONCLUSION:

Gamma knife surgery of a pituitary adenoma may cause radiation induced MR changes of the mesial temporal lobe mimicking glioma or radionecrosis and cause symptomatic epileptic seizures. The awareness of this rare complication is important to avoid unnecessary and potentially harmful diagnostic or therapeutic interventions.

Acta neurochirurgica.2006;148(8):908. Epub

Transient MR changes and symptomatic epilepsy following gamma knife treatment of a residual GHsecreting pituitary adenoma in the cavernous sinus - Comment

Kemeny, A.,

J Neurosurg. 2005 Jan;102 Suppl:119-23.

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

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OBJECT:

The authors conducted a study to determine the long-term results of gamma knife surgery for residual or recurrent growth hormone (GH)-producing pituitary adenomas and to compare the results with those after treatment of other pituitary adenomas.

METHODS:

The series consisted of 67 patients. The mean tumor diameter was 19.2 mm and volume was 5.4 cm³. The mean maximum dose was 35.3 Gy and the mean margin dose was 18.9 Gy. The mean follow-up duration was 63.3 months (range 13-142 months). The tumor resolution rate was 2%, the response rate 68.3%, and the control rate 100%. Growth hormone normalization (GH < 1.0 ng/ml) was found in 4.8%, nearly normal (< 2.0 ng/ml) in 11.9%, significantly decreased (< 5.0 ng/ml) in 23.8%, decreased in 21.4%, unchanged in 21.4%, and increased in 16.7%. Serum insulin-like growth factor (IGF)-1 was significantly decreased (IGF-1 < 400 ng/ml) in 40.7%, decreased in 29.6%, unchanged in 18.5%, and increased in 11.1%, which was almost parallel to the GH changes.

CONCLUSIONS:

Gamma knife surgery was effective and safe for the control of tumors; however, normalization of GH and IGF-1 secretion was difficult to achieve in cases with large tumors and low-dose radiation. Gamma knife radiosurgery

is thus indicated for small tumors after surgery or medication therapy when a relatively high-dose radiation is required.

Rivista Medica.2004;10(1-2):41-43. Epub

Medical management of thyrotropin-secreting pituitary adenomas

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Thyrotropin-secreting pituitary adenoma (TSH-oma) is a rare disorder, accounting for 0.5-1% of all pituitary adenomas. The great majority of TSH-omas are macroadenomas with extrasellar extension. Surgical resection is the recommended therapy, aiming at neoplastic tissue and restoring normal pituitary and thyroid function. When surgery fails, pituitary radiotherapy or gammaknife is recommended. Medical management is based on long-acting somatostatin analogs administration, such as octreotide or lanreotide treatment with these analogs will lead to a return to the euthyroid state in 80% of the cases and to tumor shrinkage in 50%. Dopamine agonists (bromocriptine, cabergoline) are not effective in the treatment of these tumors.

Yonsei Med J. 2003 Aug 30;44(4):602-7.

Radiological and hormonal responses of functioning pituitary adenomas after gamma knife radiosurgery.

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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 cm³ (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.

J Neurosurg. 2002 Sep;97(3):525-30.

Results of stereotactic radiosurgery in patients with hormone-producing pituitary adenomas: factors associated with endocrine normalization.

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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 radiosurgery 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.

J Neurosurg. 2001 Aug;95(2):285-91.

Transsphenoidal surgery and adjuvant gamma knife treatment for growth hormone-secreting pituitary adenoma.

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OBJECT:

The results of combined transsphenoidal surgery and adjuvant gamma knife surgery (GKS) for growth hormone (GH)-secreting adenoma were investigated using biochemical cure criteria for surgery and biological cure criteria for adjuvant GKS.

METHODS:

Ninety patients (42 male and 48 female patients), ranging from 11 to 75 years of age, underwent transsphenoidal surgery for GH-secreting pituitary adenoma. Preoperative and postoperative GH and insulin-like growth factor-I levels were measured, as was the postoperative GH level after the oral glucose tolerance test. Tumor size, cavernous sinus (CS) invasion, and residual tumor were evaluated using magnetic resonance (MR) imaging. Transsphenoidal microsurgery was performed, followed by adjuvant GKS when there was persistent biochemical evidence of GH hypersecretion with residual tumor detectable in the CS on MR imaging. Patients in whom GKS was contraindicated were treated with conventional radiotherapy or by medical means.

CONCLUSIONS:

The overall surgical cure rate was 57% based on recently accepted biochemical cure criteria. Patients with no CS invasion achieved a 100% cure rate, whereas patients with CS invasion achieved an 82% cure rate (14 of 17 patients) after adjuvant GKS. The combination of transsphenoidal microsurgery and adjuvant GKS is the optimal therapy for patients with GH-secreting adenoma.

Neurosurgery. 2001 Aug;49(2):284-91; discussion 291-2.

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

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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.

Stereotact Funct Neurosurg. 2000;75(2-3):123-8.

Gamma Knife radiosurgery as a primary surgical treatment for hypersecreting pituitary adenomas.

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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 cm³. 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.

Cas Lek Cesk. 2000 Dec 6;139(24):757-66.

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

[Article in Czech]

Vladyka V1, Liscák R, Simonová G, Chytka T, Novotný J Jr, Vymazal J, Marek J, Hána V, Vavros D.

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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.

No To Shinkei. 1999 Oct;51(10):895-9.

[A case of TSH-secreting pituitary adenoma associated with an unruptured aneurysm: successful treatment by two-stage operation and gamma-knife].

[Article in Japanese]

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We report a successfully treated case of invasive TSH-secreting pituitary adenoma associated with an unruptured internal carotid artery aneurysm by two-stage operation and gamma-knife radiosurgery. A 64-year-old woman was admitted to our department with a 3-year history of general fatigue and 1-year history of anxiety, palpitation and hyperhidrosis. Endocrinological examination revealed hyperthyroidism with elevated TSH, GH and somatomedin C. Magnetic resonance images demonstrated a tumor in the sella turcica which extended into the left cavernous sinus, furthermore, indicated aneurysm-like flow void at the ventral part of the left internal carotid artery. The aneurysm was confirmed by conventional angiography. Neck clipping of the aneurysm was performed through pterional approach as the first operation. One month later, at the second operation, the pituitary adenoma except for cavernous sinus portion was resected via the transsphenoidal approach. Immunohistological examination revealed positive for TSH and GH. Gamma-knife radiosurgery with a central dose of 33.3 Gy and peripheral dose of 17 Gy was carried out for residual tumor at the cavernous sinus under both MRI and CT guidance. Posttreatment course was uneventful with normalization of thyroid function at 16 months after gamma-knife. Two-stage operation and gamma-knife radiosurgery is effective for TSH-secreting adenoma extending into the cavernous sinus associated with an unruptured aneurysm.

Stereotact Funct Neurosurg. 1999;72 Suppl 1:101-10.

Gamma Knife radiosurgery for functioning pituitary adenomas.

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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.

Stereotact Funct Neurosurg. 1999;72 Suppl 1:119-24.

Gamma Knife radiosurgery for functioning pituitary microadenoma.

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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.

J Clin Endocrinol Metab. 2009 Sep;94(9):3400-7. doi: 10.1210/jc.2008-2772. Epub 2009 Jun 9.

Long-term results of stereotactic radiosurgery in secretory pituitary adenomas.

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CONTEXT:

To date, no study reported long-term follow-up results of gamma knife stereotactic radiosurgery (SR).

OBJECTIVE:

The aim of the study was to determine long-term efficacy and adverse effects of SR in secreting pituitary adenomas.

DESIGN:

We conducted a retrospective study of patients treated by SR in the center of Marseille, France, with a follow-up of at least 60 months.

PATIENTS:

A total of 76 patients were treated by SR for acromegaly (n = 43), Cushing's disease (CD; n = 18), or prolactinoma (n = 15) as a primary (n = 27) or adjunctive postsurgical treatment (n = 49).

MAIN OUTCOME MEASURES:

After withdrawal of antisecretory drugs, patients were considered in remission if they had mean GH levels below 2 ng/ml and normal IGF-I (acromegaly), normal 24-h urinary free cortisol, and cortisol less than 50 nmol/liter after low-dose dexamethasone test (CD) or two consecutive normal samplings of prolactin levels (prolactinoma).

RESULTS:

After a mean follow-up of 96 months, 44.7% of the patients were in remission. Mean time to remission was 42.6 months. Twelve patients presented late remission at least 48 months after SR. Two patients with CD presented late recurrence 72 and 96 months after SR. Forty percent of patients treated primarily with SR were in remission. Target volume and initial hormone levels were significant predictive factors of remission in univariate analysis. Radiation-induced hypopituitarism was observed in 23% patients; in half of them, hypopituitarism was observed after a mean time of 48 to 96 months. Twenty-four patients were followed for more than 120 months; rates of remission and hypopituitarism were similar to the whole cohort.

CONCLUSIONS:

SR is an effective and safe primary or adjunctive treatment in selected patients with secreting pituitary adenomas.

Stereotact Funct Neurosurg. 1998 Oct;70 Suppl 1:127-38.

Short-term endocrinological results after gamma knife surgery of pituitary adenomas.

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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).

*Acta Academiae Medicinae Shanghai.*1997;24(2):115-118. Epub

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

Wang, Enmin Pan Li, Zhou, Liangfu, Wang, Binjiang, Qin, Zhiyong, Cai, Peiwu and Dai, Jiazhong, Author affiliation: Wang-Enmin-Pan-Li, Dep. Neurosurg., Huashan Hosp., Shanghai 200040, China Wang-Binjiang, Dep. Neurosurg., Huashan Hosp., Shanghai 200040, China Cai-Peiwu, Dep. Neurosurg., Huashan Hosp., Shanghai 200040, China.

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 ~ 19.5Gy). 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, 12 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.

Sb Lek. 1995;96(4):333-8.

[Clinical neuroendocrinology].

[Article in Czech]

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An overview of research in clinical neuroendocrinology at the 3 Dept. of Internal Medicine, Charles University in Prague is reported. The research was focused on diagnosis and therapy of pituitary adenomas and on pathophysiology of some pituitary hormones. The follow up of changes in patients with acromegaly may be used as a model for possible side-effects of growth hormone therapy or doping. In acromegaly not only growth hormone serum levels but also IGF and its binding protein 3 (IGF BP-3) is used when evaluating the activity of the disease. In therapy first experience was obtained with radiosurgery using Leksell gamma knife. Thirteen year experience in using a dopaminergic agonist terguride (of Czech origin) in treatment of prolactinomas was completed. Terguride represents the treatment of first choice in patients with prolactinomas of each size, giant prolactinomas inclusively. In patients with central Cushing's disease microsurgical selective removal of pituitary adenoma is preferred. When not possible, the treatment with Leksell gamma knife is indicated with the condition of normalization of cortisol secretion with medicamentous therapy until the full effects of radiosurgery are present. Growth hormone and prolactin were proved to be immunologically active hormones, the effect of growth hormone being mediated by somatomedins. Somatomedins seem to be ubiquitous growth factors. Their presence was demonstrated even in eggs.

Stereotact Funct Neurosurg. 1993;61 Suppl 1:30-7.

The effects of Gamma Knife surgery of pituitary adenomas on tumor growth and endocrinopathies.

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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.

Neurosurgery. 1991 Nov;29(5):663-8.

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

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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.

Acta Otolaryngol. 1982 May-Jun;93(5-6):485-500.

Gamma irradiation effects on human growth hormone producing pituitary adenoma tissue. An analysis of morphology and hormone secretion in an in vitro model system.

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Irradiation-induced effects on pituitary cell morphology and secretion of growth hormone (GH) and prolactin (PRL) have been analysed using an in vitro system. Specimens for organ culture were obtained from three patients with pituitary tumours causing acromegaly but with different clinical activity of disease. Specimens were followed in vitro 1 h - 6 days after single-dose gamma irradiations (⁶⁰Co) with 70, 100 and 150 Gy, respectively. These doses are used in clinical work for the stereotactic radiosurgery of pituitary adenomas. Considerable fluctuations in hormone secretion/release occurred during the first 24 h after irradiation. Following 70 Gy single dose, the GH secretion increased slightly a few days after irradiation, having been at a minimum level 24 h after exposure. When using dose of 100 and 150 Gy, however, no such increased secretion with time after irradiation was indicated. All three tumors showed individual differences concerning irradiation-induced morphological damage. Only a minor variation occurred between specimens from the same tumour. In specimens from all tumours, irrespective of dose, minor morphological changes were observed 3-5 h after irradiation. Thereafter an individual response to irradiation became apparent. One tumour displayed maximum cell damage 24 h after irradiation with 70 Gy, showing severe oedema and damage to cell organelles. The other two adenomas were only slightly damaged following irradiation with 70, 100 and 150 Gy. Numerous morphologically normal or near-normal cells were found in all specimens from the three tumours 6 days after irradiation. An individual sensitivity to irradiation of pituitary tumours in vitro is documented. The great number of surviving pituitary tumour cells one week after irradiation--many with an intact ultrastructure and containing hormone granules--indicated an initial high degree of radioresistance.

Acromegaly

Rep Pract Oncol Radiother.2016;21(6):555-559.Epub 2016/10/11

Asymptomatic internal carotid artery occlusion after gamma knife radiosurgery for pituitary adenoma: Report of two cases and review of the literature

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BACKGROUND: Gamma knife radiosurgery is an effective and safe treatment modality in the management of pituitary adenomas. Internal carotid occlusion is a rare but possible complication of Gamma Knife Radiosurgery for lesions within the cavernous sinus. **AIM:** To stress the importance of considering the Internal carotid artery as an organ at risk in cavernous sinus invading adenomas and reduce the dose delivered to this structure whenever possible. **CASE DESCRIPTION:** We report two cases of asymptomatic occlusion of the intracavernous segment of the internal carotid artery seven years after treatment in acromegalic patients. After trans-sphenoidal surgery, residual tumour was treated with gamma knife radiosurgery. The maximal doses to the affected artery were higher than 40 Gy and the 90% isodose was close to the arterial wall. **CONCLUSION:** Every effort should be done to minimize the radiation dose to the internal carotid artery. If not possible, "hot spots" exceeding the 90% isodose close to this vessel should be avoided.

Pituitary. 2015 Jun;18(3):326-34.

Stereotactic radiosurgery for acromegaly: outcomes by adenoma subtype.

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PURPOSE:

The subtypes of somatotroph-cell pituitary adenomas have been correlated with clinical and histopathological variables. Densely granulated somatotroph-cell (DG) adenomas are typically highly responsive to somatostatin analog drugs, whereas sparsely granulated somatotroph-cell (SG) are less responsive. The aim of the study is to determine the effect of stereotactic radiosurgery (SRS) on remission and development of new pituitary deficiency according to the different subtypes of growth hormone (GH) secreting adenomas.

METHODS:

A total of 176 patients underwent SRS for acromegaly at the University of Virginia. Diagnosis of acromegaly was based on the combination of clinical features and biochemical assessment including the serum GH level, and age- and gender-matched serum insulin-like growth factor-1 level. All patients underwent endocrine and neuro-imaging evaluations before and after SRS. Histological specimens were available in 73 patients.

RESULTS:

The histopathological examination showed 34 patients had a DG adenoma, 19 had a SG adenoma, eight had a mixed DG/SG pattern, while other rare mixed subtypes were present in 12 patients. Patients who had a SG adenoma were more likely to be younger and female, and the SG adenomas appeared to be more invasive into the cavernous sinus. With a median follow-up of 67 months (range 6-188 months), 55/73 patients (75.3%) achieved remission. The median time to remission was 26 months (range 6-102 months). The actuarial remission rates in the DG adenoma group at 2, 4, and 6 years post-radiosurgery were 35.1, 71.4, and 79.3%, respectively, while those in SG adenoma group were 35.4, 73.1, and 82.1%, respectively.

CONCLUSION:

While patients who had a SG adenoma may be less responsive to medical therapy, they exhibited similar responses to SRS as patients with a DG adenoma. For SG adenomas, which respond less well to medical therapy, earlier SRS may be reasonable for consideration.

BMC Endocr Disord.2014;14(1):97. Epub 2014/12/17

Clinical experiences and success rates of acromegaly treatment: the single center results of 62 patients

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Background

This study aimed to report the clinical and outcome data from a large cohort of patients diagnosed with acromegaly and treated at our institution over a 20-year period.

Methods

Sixty-two acromegaly patients (32 women and 30 men) treated and monitored at the endocrinology polyclinic between 1984 and 2013 were enrolled in this retrospective study. Clinical features and patients' treatment outcomes were evaluated. A level of growth hormone (GH) of <2.5 ng/ml was considered as the criterion for remission, and the normal insulin-like growth factor (IGF) range was based on gender and age. The mean age at the time of diagnosis was 38.8 +/- 1.4 years, the time to diagnosis was 4.5 +/- 0.3 years, and the follow-up duration was 7.3 +/- 0.8 years.

Results

Among patients' symptoms, growth in hands and feet and typical facial dysmorphism were the most prominent (92%). The number of patients with diabetes mellitus, hypertension and hyperprolactinemia were 22 (35%), 13 (21%) and 13 (21%), respectively. Microadenomas and macroadenomas were found in eight and 54 patients, respectively. A significant correlation was found between the initial tumor diameters and GH levels ($p = 0.002$). The mean GH and IGF-1 levels were 39.18 +/- 6.1 ng/ml and 993.5 +/- 79 ng/ml, respectively. Visual field defect was found in 16 patients (32%). Thirty-one patients were treated by transsphenoidal surgery. Four of these were cured, 10 patients developed postoperative anterior pituitary hormone deficiency, and one patient developed diabetes insipidus. Twenty patients were treated by transcranial surgery, of which two were cured, while 17 patients developed postoperative anterior pituitary hormone deficiency. In total, five of the patients who were not cured after surgery were given conventional radiotherapy, of which two were cured. Four of 15 patients, on whom Gamma Knife radiosurgery was performed, were cured. Biochemical remission was achieved in 32 of 52 patients who received octreotide treatment, and in two of five patients who received lanreotide treatment.

Conclusions

The rate of surgical success in our patients was found to be low. This could be explained by an absence of experienced pituitary surgical centers or surgeons in our region, and the fact that most patients presented late at the macroadenoma stage.

J Clin Endocrinol Metab. 2014 Apr;99(4):1273-81. doi: 10.1210/jc.2013-3743. Epub 2014 Jan 28.

Stereotactic radiosurgery for acromegaly.

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CONTEXT:

The role of stereotactic radiosurgery (SRS) in acromegaly is being assessed.

OBJECTIVE:

We evaluated the efficacy and safety of SRS for patients with acromegaly. Prognostic factors related to outcomes were also analyzed.

DESIGN:

This was a retrospective study of patients treated with SRS at the University of Virginia; the data were collected from 1989 to 2012, with a median follow-up of 61.5 months.

PATIENTS:

A total of 136 patients underwent SRS for acromegaly. Diagnosis of acromegaly was based on the combination of clinical features and biochemical assessment, including the serum GH level and age- and gender-matched serum IGF-1 level. All patients underwent a complete endocrine evaluation, neuroimaging study, and ophthalmic examinations before SRS.

MAIN OUTCOME MEASURES:

After withdrawal of GH- or IGF-1-altering medications, patients who had an oral glucose tolerance test GH of < 1.0 ng/mL or normal IGF-1 were considered in remission. Post-radiosurgical hypopituitarism was defined as a decrease in one or more hormones below normal.

RESULTS:

With a median follow-up of 61.5 months, 65.4% of the patients achieved remission. The mean time to remission was 27.5 months. The actuarial remission rates at 2, 4, 6, and 8 years after radiosurgery were 31.7, 64.5, 73.4, and 82.6%, respectively. Favorable prognostic factors for remission included a higher margin radiation dose, higher maximum dose, and lower initial IGF-1 level. New pituitary hormone deficiency occurred in 43 patients (31.6%); two patients (1.5%) developed panhypopituitarism. Corresponding risk factors for new pituitary hormone deficiency were a margin dose > 25 Gy and tumor volume > 2.5 mL. Other complications included an adverse radiation effect in one patient, visual deterioration in four, and new oculomotor nerve palsy in one.

CONCLUSION:

SRS affords a reasonable rate of endocrine remission in patients with acromegaly and generally does so with a low rate of adverse effects.

Surg Neurol Int. 2013 Apr 18;4:59. doi: 10.4103/2152-7806.110658. Print 2013.

Orbital metastasis of pituitary growth hormone secreting carcinoma causing lateral gaze palsy.

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BACKGROUND:

Although pituitary adenoma is one of the most common intracranial tumors, it rarely progresses secondarily into a metastatic carcinoma. Commonalities in reported cases include subtotal resection at presentation, treatment with radiation therapy, and delayed metastatic progression. Pathologic descriptions of these lesions are varying and inconsistent.

CASE DESCRIPTION:

A 52-year-old male was diagnosed with acromegaly and pituitary tumor in 1996. He underwent four subtotal resections and five courses of stereotactic radiosurgery over 14 years. He developed left eye lateral gaze palsy, and was found to have a distant orbital metastasis with involvement of the left lateral rectus and lateral orbital wall. He underwent left orbital craniotomy via eyebrow incision for resection of this lesion. Pathologic evaluation showed a markedly elevated Ki67 level of 30%.

CONCLUSION:

While overall incidence of metastatic progression of pituitary adenoma after radiotherapy appears to be low, it appears to be a possible complication, and could be more likely in patients receiving multiple doses of radiotherapy. Our review of reported cases showed that 45/46 (97.8%) of patients developing carcinoma had prior radiation exposure. These patients may also have more aggressive pathologic characteristics of their lesions.

J Neurooncol. 2012 Aug;109(1):71-9. doi: 10.1007/s11060-012-0862-z. Epub 2012 Apr 26.

Gamma knife radiosurgery for clinically persistent acromegaly.

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

Int J Endocrinol. 2012;2012:342034. doi: 10.1155/2012/342034. Epub 2012 Feb 19.

Results of gamma knife radiosurgery in acromegaly.

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Objective. Single-session radiosurgery with Gamma Knife (GK) may be a potential adjuvant treatment in acromegaly. We analyzed the safety and efficacy of GK in patients who had previously received maximal surgical debulking at our hospital. Methods. The study was a retrospective analysis of hormonal, radiological, and ophthalmologic data collected in a predefined protocol from 1994 to 2009. The mean age at treatment was 42.3 years (range 22-67 yy). 103 acromegalic patients participated in the study. The median follow-up was 71 months (IQ range 43-107). All patients were treated with GK for residual or recurrent GH-secreting adenoma. Results. Sixty-three patients (61.2%) reached the main outcome of the study. The rate of remission was 58.3% at 5 years (95% CI 47.6-69.0%). Other 15 patients (14.6%) were in remission after GK while on treatment with somatostatin analogues. No serious side effects occurred after GK. Eight patients (7.8%) experienced a new deficit of pituitary function. New cases of hypogonadism, hypothyroidism, and hypoadrenalism occurred in 4 of 77 patients (5.2%), 3 of 95 patients (3.2%), and 6 of 100 patients at risk (6.0%), respectively. Conclusion. In a highly selected group of acromegalic patients, GK treatment had good efficacy and safety.

Int J Endocrinol. 2012;2012:821579. doi: 10.1155/2012/821579. Epub 2012 Feb 13.

Gamma knife radiosurgery for acromegaly.

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Acromegaly is debilitating disease occasionally refractory to surgical and medical treatment. Stereotactic radiosurgery, and in particular Gamma Knife surgery (GKS), has proven to be an effective noninvasive adjunct to traditional treatments, leading to disease remission in a substantial proportion of patients. Such remission holds the promise of eliminating the need for expensive medications, along with side effects, as well as sparing patients the damaging sequelae of uncontrolled acromegaly. Numerous studies of radiosurgical treatments for acromegaly have been carried out. These illustrate an overall remission rate over 40%. Morbidity from radiosurgery is infrequent but can include cranial nerve palsies and hypopituitarism. Overall, stereotactic radiosurgery is a promising therapy for patients with acromegaly and deserves further study to refine its role in the treatment of affected patients.

J Pediatr Endocrinol Metab. 2011;24(9-10):835-7.

Acrogigantism and facial asymmetry: McCune-Albright syndrome.

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McCune-Albright syndrome (MAS) is characterized by a triad of poly/monoostotic fibrous dysplasia, café-au-lait macules and hyperfunctioning endocrinopathies. Association of MAS with GH excess is rare, and in most of the instances somatotropinoma has not been documented. Treatment of patients of MAS with acromegaly is difficult because of thickened calvarium and dysplastic skull bone. We report a 17-year-old girl, who presented with cranio-facial fibrous dysplasia, café-au-lait macules and also had acromegaly due to pituitary macroadenoma, and treated with gamma knife radiosurgery.

Eur J Endocrinol. 2011 May;164(5):675-84. doi: 10.1530/EJE-10-1105. Epub 2011 Feb 7.

Long-term effects of radiotherapy on cardiovascular risk factors in acromegaly.

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OBJECTIVE:

Radiation therapy (RT) is a useful adjuvant tool for acromegalic patients not cured by surgery and/or not responding to pharmacotherapy. However, its specific effects on cardio- and cerebrovascular morbidity are still on debate.

DESIGN:

Retrospective analysis of 42 acromegalic patients cured after conventional radiotherapy (CRT, n=31) or radiosurgery by gamma-knife (GKRS, n=11) followed for a median period of 16.5 years (range: 2-40). Totally, 56 patients cured by surgery alone, with similar GH/IGF1 levels and duration of disease remission, served as control group.

METHODS:

Changes in cardiovascular risk factors, such as body mass index, glucose metabolism, insulin resistance, blood pressure, and lipid profile (pre-defined primary end point) and occurrence of new major cardio- and cerebrovascular events (secondary end point) during follow-up.

RESULTS:

The number of obese, hypertensive, and dyslipidemic subjects increased over time only in patients cured with RT. In contrast, the glucose response to the oral glucose tolerance test and the percentage of subjects with glucose alterations improved only in controls. As expected, the percentage of patients with pituitary failure was deeply higher among RT patients than among controls (86 vs 30%, $P < 0.0005$). Despite these findings, a similar number of RT patients and controls developed major cardio- or cerebrovascular events (4/42 vs 3/56, P : NS). No differences were found between CRT and GKRS subgroups.

CONCLUSIONS:

Previous RT seems to be associated with a worse metabolic profile in acromegalic patients studied after a long-term follow-up. Nevertheless, a direct link between RT and cardiovascular events remains to be proven.

J Clin Neurosci. 2011 Dec;18(12):1616-20. Epub 2011 Oct 15.

Gammaknife radiosurgery in patients with acromegaly.

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

Neurosurg Focus. 2010 Oct;29(4):E12.

Radiation treatment strategies for acromegaly.

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The high morbidity and mortality associated with acromegaly can be addressed with multiple treatment modalities, including surgery, medicines, and radiation therapy. Radiation was initially delivered through conventional fractionated radiotherapy, which targets a wide area over many treatment sessions and has been shown to induce remission in 50%–60% of patients with acromegaly. However, conventional fractionated radiotherapy takes several years to achieve remission in patients with acromegaly and carries a risk of hypopituitarism that may limit its use. Stereotactic radiosurgery, of which there are several forms, including Gamma Knife surgery, CyberKnife therapy, and proton beam therapy, offers slightly attenuated efficacy but achieves remission in less time and provides more precise targeting of the adenoma with better control of the dose of radiation received by adjacent structures such as the pituitary stalk, pituitary gland, optic chiasm, and cranial nerves in the cavernous sinus. Of the forms of stereotactic radiosurgery, Gamma Knife surgery is the most widely used and, because of its long-term follow-up in clinical studies, is the most likely to compete with medical therapy for first-line adjuvant use after resection. In this review, the authors outline the major modes of radiation therapies in clinical use today, and they critically assess the feasibility of these modalities for acromegaly treatment. Acromegaly is a multisystem disorder that demands highly specialized treatment protocols including neurosurgical and endocrinological intervention. As more efficient forms of pituitary radiation develop, acromegaly treatment options may continue to change with radiation therapies playing a more prominent role.

J Neurosurg. 2010 Dec;113 Suppl:149-152.

Predictors of outcome following Gamma Knife surgery for acromegaly.

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OBJECT:

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

METHODS:

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

RESULTS:

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

CONCLUSIONS:

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

Clin Endocrinol (Oxf). 2009 Dec;71(6):846-52. Epub 2009 Mar 28.

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

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OBJECTIVE:

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

DESIGN AND PATIENTS:

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

MAIN OUTCOME MEASURES:

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

RESULTS:

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

CONCLUSIONS:

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

Pituitary. 2009;12(1):3-10. doi: 10.1007/s11102-007-0078-y.

Radiotherapy and radiosurgery in acromegaly.

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Growth-hormone hypersecretion, acromegaly, is associated with reduced life expectancy. First line treatment remains surgery, but remission rates vary between 50% and 90%. In case of lack of surgical remission or recurrence, somatostatin agonists can be proposed. However, about 30% of patients are partially or totally resistant to this treatment. The growth hormone receptor antagonist pegvisomant currently needs more prolonged follow-up studies. Conventional radiotherapy and radiosurgery are two radiation treatment modalities that can be proposed to these resistant patients. Reported rates of remission for conventional radiotherapy range between 50% and 60% in patients with acromegaly, with a time to remission delayed by several years, and adverse effects including high rates of hypopituitarism. This treatment could be proposed to patients with aggressive adenomas, in whom surgery cannot allow biochemical control. In contrast, studies on stereotactic radiosurgery reported lower rates of remission, with faster growth hormone hypersecretion decline, and a lower risk of adverse effects. However, this latter technique requires a well defined target volume, which limits its indications. The high precision of this technique makes it possible to be used as an alternative primary treatment to surgery. We reviewed major advantages and drawbacks of each of these techniques, based on recent studies to try to define their respective indications in the therapeutic algorithm of acromegaly.

J Clin Endocrinol Metab. 2008 Jul;93(7):2546-52. doi: 10.1210/jc.2008-0135. Epub 2008 Apr 15.

The role of stereotactic radiotherapy in patients with growth hormone-secreting pituitary adenoma.

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CONTEXT:

Single-session stereotactic radiotherapy (SR) may be a potential adjuvant treatment in acromegaly.

OBJECTIVE:

We analyzed the safety and efficacy of SR in patients who had previously received maximal surgical debulking at our center.

DESIGN:

The study was a retrospective analysis of hormonal, radiological, and ophthalmologic data collected in a predefined protocol from 1994 through 2006.

SETTING:

The study was performed at a university hospital.

PATIENTS:

Eighty-three acromegalic patients, 52 women and 31 men, with a mean age of 42.6 +/- 1.2 yr, participated in the study. The median follow-up was 69 months (interquartile range 44-107 months).

INTERVENTION:

The patients were treated with SR for residual or recurrent GH-secreting adenoma.

MAIN OUTCOME MEASURE:

Normalization of age- and sex-adjusted IGF-I levels together with a basal GH level below 2.5 microg/liter without concomitant GH-suppressive drugs was the goal of therapy.

RESULTS:

Fifty patients (60.2%) reached the main outcome of the study. The rate of remission was 52.6% at 5 yr [95% confidence interval (CI) 40.6-64.6%]. Another 13 patients (15.7%), who were resistant to somatostatin analogs, were in remission after SR. Multivariate analysis showed that low basal GH and IGF-I levels were associated with a favorable outcome. No serious side effects occurred after SR. The 5-yr cumulative risk of new onset hypogonadism, hypothyroidism, or hypoadrenalism was 3.6% (95% CI 0-8.6%), 3.3% (95% CI 0-7.7%), and 4.9% (95% CI 0-10.4%), respectively.

CONCLUSION:

In a highly selected group of acromegalic patients, SR treatment had good efficacy and safety. This may lead to reconsider the role of SR in the therapeutic algorithm of acromegaly.

Rev Endocr Metab Disord. 2008 Mar;9(1):67-70. doi: 10.1007/s11154-007-9064-y.

Surgery for acromegaly: evolution of the techniques and outcomes.

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This paper presents an overview of the evolution of pituitary surgery for acromegaly. It begins with the first case, attempted in 1893, through the initial transsphenoidal successes in 1907-1910, to the development of effective craniotomy approaches, and ultimately to the resurrection of the transsphenoidal approach in the 1970s and thereafter. Today, the minimally endoscopic transnasal endoscopic approach is fast becoming the norm. Indications for surgery include active acromegaly, visual loss and other forms of mass effect, pituitary tumor apoplexy, and failure of other therapies (medical, radiation). Contraindications include advanced age, debility or other medical conditions increasing the risk of general anaesthesia or surgery. Surgery for acromegaly has the advantage of immediate lowering of the growth hormone excess, with endocrine remission rates of 70% for microadenomas and 50% for macroadenomas. When surgery fails to obtain remission, a program of therapy is designed for the patient to include adjunctive medical therapy (dopamine agonists, somatostatin analogs, and growth hormone receptor antagonists), radiation therapy or radiosurgery (Gamma knife, Cyberknife, etc.).

Neurosurgery. 2008 Jun;62(6):1262-9; discussion 1269-70. doi: 10.1227/01.neu.0000333297.41813.3d.

Gamma knife radiosurgery for acromegaly: outcomes after failed transsphenoidal surgery.

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OBJECTIVE:

This study evaluates the safety and efficacy of gamma knife radiosurgery (GKRS) in patients with a growth hormone-secreting adenoma.

METHODS:

A retrospective review of data collected from a prospective database of GKRS patients between January 1988 and September 2006 was performed in patients with acromegaly. Successful endocrine outcome was defined as normalization of the insulin-like growth factor level. Tumor volume was also assessed. At least 18 months of follow-up was available in 95 patients who received radiosurgery during the study period. Mean endocrine follow-up was 57 months (range, 18-168 mo).

RESULTS:

Normal insulin-like growth factor levels were achieved in 50 patients (53%) at an average time of 29.8 months after radiosurgery (median, 23.5 mo). A decrease in tumor volume control was achieved in 83 (92%) of 90 patients. Five patients (6%) had no change in tumor volume, and two patients (2%) had an increase in tumor volume. New endocrine deficiencies developed in 32 patients (34%). Four patients developed new-onset partial visual acuity deficits; three of these patients had received previous conventional fractionated radiation therapy.

CONCLUSION:

GKRS is a complementary treatment for recurrent or residual growth hormone-secreting pituitary adenomas. Although infrequent, tumor growth, new-onset pituitary hormone deficiency, recurrence, and neurological dysfunction require careful clinical, radiological, and endocrinological follow-up.

Eur J Endocrinol. 2007 Sep;157(3):255-63.

Gamma knife stereotactic radiosurgery for acromegaly.

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BACKGROUND:

Gamma knife radiosurgery (GKR) is an adjuvant treatment for acromegaly if surgery fails to normalize GH hypersecretion.

OBJECTIVE:

To examine the effect of GKR on tumor growth and hypersecretion, and to characterize the adverse effect of this treatment.

DESIGN:

Cross-sectional follow-up study. First, retrospective data pre- and post-GKR were collected. PATIENTS then underwent a predefined survey including radiological, endocrinological, ophthalmological, and neurosurgical evaluation.

SETTING:

Norwegian National Center for gamma knife treatment.

PATIENTS:

Sixty-one patients treated with GKR for acromegaly. Out of 55, 53 living patients underwent a detailed survey. The mean follow-up was 5.5 years. No patient was lost to follow-up.

RESULTS:

Tumor growth was stopped in all patients. At 3, 5, and 10 years after GKR, 45, 58, and 86% of patients had normal IGF-I levels. Consecutive hormone value analysis showed that patients receiving GH-suppressive medication had a more rapid decline in hypersecretion than those who did not receive such medication. Evaluated by survey baseline values alone, non-elevated IGF-I and GH levels below 5 mIU/l were found in 38%. GH-suppressive medication was terminated in 16 out of 40 patients following GKR. Nine out of 53 surveyed patients (17%) had normal IGF-I and GH nadir below 2.6 mIU/l at glucose tolerance tests, while not on hormone-suppressive medication. Two patients developed minor visual field defects. Eight patients started hormone substitution therapy during the follow-up period.

CONCLUSION:

GKR is an effective adjuvant treatment for residual acromegaly, carrying few side effects.

J Neurosurg. 2007 May;106(5):833-8.

Radiosurgery of growth hormone-producing pituitary adenomas: factors associated with biochemical remission.

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OBJECT:

The authors reviewed outcomes after stereotactic radiosurgery for patients with acromegaly and analyzed factors associated with biochemical remission.

METHODS:

Retrospective analysis was performed for 46 consecutive cases of growth hormone (GH)-producing pituitary adenomas treated by radiosurgery between 1991 and 2004. Biochemical remission was defined as a fasting GH less than 2 ng/ml and a normal age- and sex-adjusted insulin-like growth factor-I (IGF-I) level while patients were not receiving any pituitary suppressive medications. The median follow up after radiosurgery was 63 months (range 22-168 months). Twenty-three patients (50%) had biochemical remission documented at a median of 36

months (range 6-63 months) after one radiosurgical procedure. The actuarial rates of biochemical remission at 2 and 5 years after radiosurgery were 11 and 60%, respectively. Multivariate analysis showed that IGF-I levels less than 2.25 times the upper limit of normal (hazard ratio [HR] 2.9, 95% confidence interval [CI] 1.2-6.9, $p = 0.02$) and the absence of pituitary suppressive medications at the time of radiosurgery (HR 4.2, 95% CI 1.4-13.2, $p = 0.01$) correlated with biochemical remission. The incidence of new anterior pituitary deficits was 10% at 2 years and 33% at 5 years.

CONCLUSIONS:

Discontinuation of pituitary suppressive medications at least 1 month before radiosurgery significantly improved endocrine outcomes for patients with acromegaly. Patients with GH-producing pituitary adenomas should not undergo further radiation therapy or surgery for at least 5 years after radiosurgery because GH and IGF-I levels continue to normalize over that interval.

Clin Endocrinol (Oxf). 2006 May;64(5):588-95.

Gamma knife radiosurgery for acromegaly--long-term experience.

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OBJECTIVE:

The Leksell gamma knife (LGK) is one of the treatment options for pituitary adenomas. We report on our long-term experience treating acromegaly using LGK.

DESIGN:

Since 1993 we have followed 96 acromegaly patients through periods of from 12 to 120 months. The mean follow-up period was 53.7 +/- 26.8 months. Seventy-two patients were treated with neurosurgery prior to LGK; for 24 LGK was the primary treatment. Thirteen patients were irradiated twice, due to persistent activity of the adenoma or its residue. Pituitary functions were tested at 6-month intervals, post-irradiation. The target tumour volume for radiosurgery was between 93.3 and 12 700 mm³ (median 1350 mm³).

RESULTS:

Fifty per cent of the patients achieved mean GH < 2.5 microg/l within 42 months, normalized their IGF-I within 54 months, and achieved GH suppression in the oral glucose tolerance test (oGTT) < 1 microg/l with normal IGF-I within 66 months. LGK effectiveness was dependent on initial adenoma hormonal activity (GH and IGF-I serum levels), not on the size of the adenoma. Patients with primary neurosurgery followed by LGK irradiation had better outcomes than those with LGK alone. Irradiation arrested all adenoma growth, causing tumour shrinkage in 62.3% of patients. Twenty-six developed hypopituitarism when irradiated by 15 Gy (or more) on functional peritumoral pituitary tissue. No hypopituitarism appeared using lower doses.

CONCLUSIONS:

In acromegaly, LGK is a useful adjunct to primary neurosurgery when treating post-surgical residues because it can limit the duration of medical therapy. It can be used as a primary therapy when neurosurgery is not possible.

Nature Clinical Practice Endocrinology and Metabolism.2006;2(8):418-419. Epub

Leksell Gamma Knife® radiotherapy in patients with acromegaly

J Clin Neurosci. 2004 May;11(4):418-21.

Gamma knife radiosurgery for GH-secreting microadenoma with empty sella.

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We report a case of a growth hormone secreting microadenoma associated with empty sella treated by gamma knife radiosurgery and we evaluate the effectiveness of radiosurgery for this lesion. A 58-year-old female complained of an acromegalic appearance for 10 years. Magnetic resonance imaging revealed an enlarged sella floor with a compressed, but slightly enlarged pituitary gland. Serum GH values were 8.52 ng/ml. From these results, we diagnosed the presence of a GH-secreting pituitary microadenoma with empty sella. Stereotactic gamma knife radiosurgery was performed to treat the adenoma. The treatment dose was 30 Gy for the tumour margin (50% isodose). The patient was monitored for 5 years without any reported problem. Serum GH values were gradually decreased to 4.1 and 3.5 ng/ml at 1.6 and 3 years. Serum GH values at 5 years after radiosurgery were 1.8 ng/ml within 2 h after glucose load and serum IGF-1 was normalized. We conclude that gamma knife radiosurgery can be an useful alternative treatment modality for GH-secreting adenoma with empty sella in the selected patients when surgery is contraindicated as the primary treatment.

Horm Res. 2004;62 Suppl 3:79-92.

Treatment of acromegaly.

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Mortality is increased in individuals with acromegaly unless serum growth hormone (GH) levels are below 2 microg/l and serum insulin-like growth factor (IGF)-I levels are normal following treatment. These combined criteria have been used to define remission of the disorder in this review. Transsphenoidal surgery achieves remission targets in an average of 55% of patients. For those not in remission following surgery, options include repeat surgery or use of adjuvant therapy. Fractionated external beam pituitary radiotherapy achieves 10-year remission rates of 47% but leaves patients exposed to excess GH until remission occurs. Stereotactic radiotherapy and gamma knife radiosurgery achieve remission rates of 40% over 3 years, and dopamine agonists produce remission in about 20% of patients. Somatostatin analogues induce remission in 59% of patients within the first year of treatment. The GH receptor antagonist pegvisomant leads to remission in 90% of patients, using IGF-I levels for assessment. Optimal treatment for a patient with acromegaly thus depends on the likely efficacy of treatment, cost, surgical skill, severity of side effects, tolerability, control of tumour growth, and improvement in complications related to tumour mass. A primary surgical approach, followed by medical therapy for those not in remission, remains the preferred option in most centres.

Zhonghua Yi Xue Za Zhi. 2003 Dec 10;83(23):2045-8.

[Efficacy of gamma knife radiosurgery in treatment of growth hormone-secreting pituitary adenoma].

[Article in Chinese]

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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 cm³ (0.11-12.7 cm³) 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%). Amblyopia appeared in one patient. No other complication was found during the follow-up.

CONCLUSION:

GKS is safe and effective on the treatment of GH-secreting pituitary adenoma.

J Clin Endocrinol Metab. 2003 Jul;88(7):3105-12.

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

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Stereotactic radiosurgery by gamma-knife (GK) is an attractive therapeutic option after failure of microsurgical removal in patients with pituitary adenoma. In these tumors or remnants of them, it aims to obtain the arrest of cell proliferation and hormone hypersecretion using a single precise high dose of ionizing radiation, sparing surrounding structures. The long-term efficacy and toxicity of GK in acromegaly are only partially known. Thirty acromegalic patients (14 women and 16 men) entered a prospective study of GK treatment. Most were surgical failures, whereas in 3 GK was the primary treatment. Imaging of the adenoma and target coordinates identification were obtained by high resolution magnetic resonance imaging. All patients were treated with multiple isocenters (mean, 8; range, 3-11). The 50% isodose was used in 27 patients (90%). The mean margin dose was 20 Gy (range, 15-35), and the dose to the visual pathways was always less than 8 Gy. After a median follow-up of 46 months (range, 9-96), IGF-I fell from 805 micro g/liter (median; interquartile range, 640-994) to 460 micro g/liter (interquartile range, 217-654; P = 0.0002), and normal age-matched IGF-I levels were reached in 7 patients (23%). Mean GH levels decreased from 10 micro g/liter (interquartile range, 6.4-15) to 2.9 micro g/liter (interquartile range, 2-5.3; P < 0.0001), reaching levels below 2.5 micro g/liter in 11 (37%). The rate of persistently pathological hormonal levels was still 70% at 5 yr by Kaplan-Meier analysis. The median volume was

1.43 ml (range, 0.20-3.7). Tumor shrinkage (at least 25% of basal volume) occurred after 24 months (range, 12-36) in 11 of 19 patients (58% of assessable patients). The rate of shrinkage was 79% at 4 yr. In no case was further growth observed. Only 1 patient complained of side-effects (severe headache and nausea immediately after the procedure, with full recovery in a few days with steroid therapy). Anterior pituitary failures were observed in 2 patients, who already had partial hypopituitarism, after 2 and 6 yr, respectively. No patient developed visual deficits. GK is a valid adjunctive tool in the management of acromegaly that controls GH/IGF-I hypersecretion and tumor growth, with shrinkage of adenoma and no recurrence of the disease in the considered observation period and with low acute and chronic toxicity.

Pituitary. 2002;5(3):185-96.

Current status and future opportunities for controlling acromegaly.

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Growth-hormone (GH) secreting adenomas, including acromegaly, account for approximately one-sixth of all pituitary adenomas and are associated with mortality rates at least twice that of the general population. The ultimate goal of therapy for acromegaly is normalization of morbidity and mortality rates achieved through removal or reduction of the tumor mass and normalization of insulin-like growth factor I (IGF-I) levels. Previously published efficacy results of current treatment modalities (surgery, conventional radiation, and medical therapy with dopamine agonists and somatostatin analogs) are often difficult to compare because of the different criteria used to define cure (some of which are now considered inadequate). For each of these modalities, pooled data from a series of acromegaly studies were reviewed for rates of IGF-I normalization, a currently accepted definition of cure. The results showed overall cure rates of approximately 10% for bromocriptine, 34% for cabergoline, 36% for conventional radiation, 50-90% for surgery for microadenomas and less than 50% for macroadenomas, and 54-66% for octreotide. These cure rates based on IGF-I normalization are generally less than those reported for cure based solely on GH levels. Novel new therapies for acromegaly include the somatostatin analog, lanreotide, Gamma Knife radiosurgery, and pegvisomant, the first in its class of new GH receptor antagonists. Although it does not appear that Gamma Knife radiosurgery results in significantly higher cure rates or fewer complications, it does provide a notable improvement in delivery compared with conventional radiation. Early studies have reported IGF-I normalization in 48% of lanreotide-treated patients and up to 97% of pegvisomant-treated.

Pituitary. 2001 Sep;4(4):223-30.

Gamma knife radiosurgery in the management of patients with acromegaly: a review.

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Although acromegaly is a rare disease, the need for an effective treatment that is able to induce biochemical cure is an extremely important issue. Unsuccessfully treated acromegaly is associated with increased morbidity and an age-corrected mortality so that early and aggressive therapy to normalize hormonal levels should be instituted at diagnosis. Ideally, the growth hormone-secreting adenoma should be completely resected, with preservation or subsequent restoration of pituitary function. Patients with recurrence or failure after surgery are treated with a second surgery, medical, radiation treatment, or combined modality treatment. Stereotactic radiosurgery with gamma knife allows the delivery of focused radiation in a single session to the pituitary tumor that delivers a more biologically effective dose to the tumor than fractionated radiotherapy. Its use as a primary or adjuvant treatment for acromegalics may be more cost effective than medical treatment in these patients. Although it seems to be very effective in controlling growth and secretion of the growth hormone-secreting pituitary adenomas, there is a chance that some major risks from gamma knife radiosurgery might occur. This article will review the role that gamma knife radiosurgery might have in patients with acromegaly.

Stereotact Funct Neurosurg. 2001;76(3-4):213-7.

Gamma knife radiosurgery for growth hormone-secreting pituitary adenomas invading the cavernous sinus.

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The authors assessed whether gamma knife radiosurgery is effective for patients with acromegaly where the pituitary tumors invaded the cavernous sinus. Radiosurgery was performed on 9 patients (average of 20 Gy to the tumor margin), 8 of whom had already undergone transsphenoidal surgery and/or craniotomy with occasional medication of octreotide to reduce tumor size as well as hormonal levels. All tumors have been well controlled so far with follow-up periods ranging from 12 to 69 months (mean: 42). No complications occurred. Forty percent of the patients showed hormonal normalization at 2 years, with the median being 31 months. Similarly, 50% of the patients demonstrated normalization of GH and IGF-I at 36 months. We conclude that gamma knife radiosurgery is a safe and effective tool to treat these tumors invading the cavernous sinus.

J Neurosurg. 2000 Dec;93 Suppl 3:6-9.

Radiosurgery for growth hormone-producing pituitary adenomas.

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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.

J Clin Endocrinol Metab. 2000 May;85(5):2068-71.

Outcome of radiotherapy for acromegaly using normalization of insulin-like growth factor I to define cure.

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Abstract

Radiation therapy (RT) has traditionally been considered a useful additional therapy for patients with acromegaly not achieving biochemical remission after surgery. However, recent evidence has suggested that RT is not curative in most patients with acromegaly when normalization of the serum insulin-like growth factor I (IGF-I) level is used to define remission. Therefore, we evaluated the success of RT based on IGF-I level in the 47 patients who received RT as part of their treatment from the cohort of 161 patients with acromegaly seen by us between 1981 and 1999. Four patients in whom no post-RT IGF-I level was available were excluded from the analysis. Of the remaining 43 patients, 32 patients received external beam RT, 6 received fractionated stereotactic radiosurgery, 4 received gamma-knife RT, and 1 received proton beam RT. The most recent IGF-I levels in these 43 patients, obtained a mean of 5.2 yr post-RT (range, 0.8-13.2 yr), were compared to age-adjusted normal ranges. IGF-I levels were normal in 17 patients (39.5%) without the addition of medical therapy. The percentage of patients with a normal IGF-I level generally increased with time post-RT; 27% of patients less than 6 yr post-RT, but 69.2% of patients 6 yr or more post-RT had normal IGF-I levels. Using the more traditional criterion for cure, a random GH measurement, 74% of patients had a GH level below 5 ng/mL, and 44% had a GH level below 2.5 ng/mL and would have been considered in remission based on these criteria. We conclude that with time RT remains a useful adjunctive treatment for many patients with acromegaly. RT should be considered along with appropriate medical therapy in selected patients who do not achieve normalization of IGF-I level after surgery or for those resistant to medical therapy.

J Clin Endocrinol Metab. 2000 Mar;85(3):1287-9.

Octreotide may act as a radioprotective agent in acromegaly.

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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).

Tidsskr Nor Laegeforen. 2000 Sep 10;120(21):2534-8.

[Acromegaly--diagnosis and treatment].

[Article in Norwegian]

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BACKGROUND:

Acromegaly is a rare but clinically important disease caused by growth hormone hypersecretion, usually from a pituitary adenoma. The condition is associated with increased morbidity and mortality.

MATERIAL AND METHODS:

The prevalence of acromegaly is estimated to be 4-6 cases per million per year. The diagnosis is based on glucose-suppressed plasma growth hormone. When the diagnosis is confirmed, MR imaging of the pituitary gland is performed.

RESULTS:

Standard treatment is transsphenoidal microsurgery; however, radicality is often difficult because of extensive tumour growth. Preoperative administration of somatostatin analogues may improve the surgical outcome.

INTERPRETATION:

We have initiated a randomized, prospective study to elucidate this adjuvant treatment. Somatostatin analogues are required in the case of postoperative activity. This treatment is without tachyphylaxis and has few side effects. Alternatively, dopamine agonists such as bromocriptine can be used, especially in mixed tumours coproducing prolactin. Newer, more specific dopamine agonists are currently being evaluated. Radiation therapy may be required in large, unresectable tumours, but the effects are slow-acting, and almost all patients develop hypopituitarism. Gamma knife radiosurgery seems promising for stopping tumour growth as well as for decreasing excessive hormone production. However long-time follow-up results are so far lacking.

J Neurol Neurosurg Psychiatry. 1999 Feb;66(2):244.

Radiosurgically treated acromegaly.

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1Department of Neurosurgery, Faculty of Medicine, University of Tokyo, Japan.

Pituitary. 1999 Jun;2(1):71-7.

Role of gamma knife radiosurgery in acromegaly.

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Stereotactic radiosurgery with the Gamma Knife allows the delivery of focused radiation in a single session from a Cobalt-60 source to a pituitary tumor with little radiation to surrounding normal brain tissue. At this time the major role for Gamma Knife radiosurgery in acromegaly is for the treatment of failed pituitary surgery although it may also be used as primary treatment for patients unwilling or unsuitable, for medical reasons, to undergo transsphenoidal surgery. The major risk from Gamma Knife radiosurgery appears to be radiation damage to the visual pathways, but this can be obviated by limiting the radiation dose to the optic chiasm under 10 Gy. In contrast, the neuronal and vascular structures running in the cavernous sinus are much less radiosensitive

allowing an ablative dose to be administered to tumors showing lateral invasion and impinging on cranial nerves III, IV, V and VI. Gamma Knife radiosurgery appears to produce effects in GH secreting tumors faster than with fractionated radiotherapy without the potential long-term risk of developing a second extrapituitary brain tumor as well as the neuropsychiatric effects associated with conventional radiation administration.

J Neurosurg. 1998 Jun;88(6):1002-8.

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

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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.

Baillieres Clin Endocrinol Metab. 1995 Apr;9(2):271-314.

Clinical features and differential diagnosis of pituitary tumours with emphasis on acromegaly.

Hennessey JV1, Jackson IM.

1Division of Endocrinology, Brown University School of Medicine/Rhode Island Hospital, Providence 02903, USA. Pituitary adenomas are frequently encountered, benign intracranial tumours. Clinically classified according to their capacity to produce and secrete hormones, pituitary tumours are diagnosed from the clinical manifestations and biochemical findings of specific pituitary hormone overproduction or of impaired pituitary function due to pressure on normal pituitary cells, the pituitary stalk or the hypothalamus. Additionally, the tumour may result in neurological manifestations due to its effect as an intracranial space-occupying lesion. Pituitary adenomas may present acutely with pituitary apoplexy after intrapituitary haemorrhage or infarction. The subsequent hypofunction of the pituitary with concomitant neurological sequelae of an expanding intracranial mass are often associated with excruciating headache, diplopia and visual field defects. Gradually developing neurological deficits or secondary endocrine failure over several years may precede the recognition of non-secretory tumours (30-40% of pituitary adenomas) as well as some of the hormone-producing adenomas, especially when they expand beyond the confines of the sella turcica. Asymptomatic masses occur in the pituitary in 5-27% of unselected autopsy series. About 10-20% of pituitaries imaged as part of a brain study contain lesions 'consistent with a pituitary adenoma', with about half being pituitary adenomas ('incidentalomas'). Many advocate screening such cases for a wide spectrum of pituitary function abnormalities. Clinical judgement should be utilized to determine the extent of the work-up and the frequency of follow-up. Acromegaly, a clinical syndrome caused by excess growth hormone secretion, accounts for one-sixth of resected pituitary tumours. This disorder leads to chronic progressive disability and a shortened life span, with approximately 50% of untreated acromegalic patients experiencing premature death. The prevalence of acromegaly has been estimated to range from 50 to 70 per million, with the age of diagnosis usually between the third and fifth decades. Conditions associated with acromegaly include glucose intolerance, diabetes mellitus, lipid abnormalities, cholelithiasis, goitre, and hyperthyroidism, respiratory complications, hypertension, cardiovascular disease, and calcium metabolism abnormalities. An association between acromegaly and cancer, especially of the colon, is now recognized. Epidemiological series have indicated that cancer of the colon, breast and other types of malignancy are a cause of death with increased frequency in acromegalics compared with expected rates. Hypopituitary symptoms secondary to the mass effect of macroadenomas in acromegalic

patients are common. Among premenopausal women, menstrual irregularities and galactorrhoea have been reported in 40-70%, while more than half of the men complain of impotence and decreased libido.

Cushing Disease

Pituitary.2014;Epub 2014/07/11

Gamma knife radiosurgery for Cushing's disease and Nelson's syndrome

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Purpose

This paper presents our 18 years of experience in treating ACTH secreting adenomas (Cushing's disease and Nelson's syndrome) using the Leksell gamma knife (LGK) irradiation.

Methods

Twenty-six patients with Cushing's disease were followed-up after LGK irradiation for 48-216 months (median 78 months). Seventeen patients had undergone previous surgery, in nine patients LGK irradiation was the primary therapy. Furthermore, 14 patients with Nelson's syndrome were followed-up for 30-204 months (median 144 months).

Results

LGK treatment resulted in hormonal normalization in 80.7 % of patients with Cushing's disease. Time to normalization was 6-54 months (median 30 months). The volume of the adenoma decreased in 92.3 % (in 30.7 % disappeared completely). There was no recurrence of the disease. In all 14 patients with Nelson's syndrome ACTH levels decreased (in two patients fully normalized) their ACTH levels. When checked up 5-10 years after irradiation regrowth of the adenoma was only detected in one patient (9.1 %), in 27.3 % adenoma volume remained unchanged, in 45.4 % adenoma volume decreased and in 18.2 % adenoma completely disappeared. Hypopituitarism did not develop in any patient where the critical dose to the pituitary and distal infundibulum was respected. Conclusion LGK radiation represents an effective and well-tolerated option for the treatment of patients with Cushing's disease after unsuccessful surgery and may be valuable even as a primary treatment in patients who are not suitable for, or refuse, surgery. In the case of Nelson's syndrome it is possible to impede tumorous growth and control the size of the adenoma in almost all patients.

J Neurol Surg A Cent Eur Neurosurg. 2014 Mar;75(2):91-7. doi: 10.1055/s-0033-1345688. Epub 2013 Aug 21.

Repeated transsphenoidal surgery or gamma knife radiosurgery in recurrent cushing disease after transsphenoidal surgery.

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BACKGROUND:

This study compared Gamma knife radiosurgery (GKRS) and repeated transsphenoidal adenomectomy (TSA) to find the best approach for recurrence of Cushing disease (CD) after unsuccessful first TSA.

MATERIAL AND METHODS:

Fifty-two patients with relapse of CD after TSA were enrolled and randomly underwent a second surgery or GKRS as the next therapeutic approach. They were followed for a mean period of 3.05 ± 0.8 years by physical examination and hormone measurement as well as magnetic resonance imaging.

RESULTS:

No significant difference was observed in sex ratio, mean age, adenoma type, follow-up duration, and initial hormone level between the two groups. No significant relationship was found between preoperative 24-hour free urine cortisol and disease-free months or tumor volume among both groups. Our statistical analysis showed higher recurrence-free interval in the GKRS group compared with TSA group.

CONCLUSION:

With longer recurrence-free interval, GKRS could be considered a good treatment alternative to repeated TSA in recurrent CD.

J Neurol Surg A Cent Eur Neurosurg. 2014 Mar;75(2):91-7. Epub 2013 Aug 21.

Repeated transsphenoidal surgery or gamma knife radiosurgery in recurrent cushing disease after transsphenoidal surgery.

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7Department of Radiology, Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran.

BACKGROUND:

This study compared Gamma knife radiosurgery (GKRS) and repeated transsphenoidal adenomectomy (TSA) to find the best approach for recurrence of Cushing disease (CD) after unsuccessful first TSA.

MATERIAL AND METHODS:

Fifty-two patients with relapse of CD after TSA were enrolled and randomly underwent a second surgery or GKRS as the next therapeutic approach. They were followed for a mean period of 3.05 ± 0.8 years by physical examination and hormone measurement as well as magnetic resonance imaging.

RESULTS:

No significant difference was observed in sex ratio, mean age, adenoma type, follow-up duration, and initial hormone level between the two groups. No significant relationship was found between preoperative 24-hour free urine cortisol and disease-free months or tumor volume among both groups. Our statistical analysis showed higher recurrence-free interval in the GKRS group compared with TSA group.

CONCLUSION:

With longer recurrence-free interval, GKRS could be considered a good treatment alternative to repeated TSA in recurrent CD.

J Neurosurg. 2013 Dec;119(6):1484-5; discussion 1485. doi: 10.3171/2013.4.JNS13642. Epub 2013 Aug 9.

Cushing's disease and stereotactic radiosurgery.

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Results of gamma knife surgery for Cushing's disease. [J Neurosurg. 2013]

J Neurosurg. 2013 Dec;119(6):1486-92. doi: 10.3171/2013.7.JNS13217. Epub 2013 Aug 9.

Results of gamma knife surgery for Cushing's disease.

Sheehan JP1, Xu Z, Salvetti DJ, Schmitt PJ, Vance ML.

1Departments of Neurological Surgery and.

OBJECT:

Cushing's disease is a challenging neuroendocrine disorder. Although resection remains the primary treatment option for most patients, the disease persists if there is residual or recurrent tumor. Stereotactic radiosurgery has been used to treat patients with persistent Cushing's disease after a prior resection. The authors report on the long-term risks and benefits of radiosurgery for Cushing's disease.

METHODS:

A retrospective review of a prospectively collected database of radiosurgery patients was undertaken at the University of Virginia. All patients with Cushing's disease treated with Gamma Knife surgery (GKS) were identified. Those without at least 12 months of clinical and radiological follow-up were excluded from this analysis. Rates of endocrine remission, tumor control, and adverse events were assessed. Statistical methods were used to identify favorable and unfavorable prognostic factors.

RESULTS:

Ninety-six patients with the required follow-up data were identified. The mean tumor margin dose was 22 Gy. The median follow-up was 48 months (range 12-209.8 months). At the last follow-up, remission of Cushing's disease occurred in 70% of patients. The median time to remission among all patients was 16.6 months (range

1-165.7 months). The median time to remission in those who had temporarily stopped taking ketoconazole at the time of GKS was 12.6 months, whereas it was 21.8 months in those who continued to receive ketoconazole ($p < 0.012$). Tumor control was achieved in 98% of patients. New loss of pituitary function occurred in 36% of patients. New or worsening cranial neuropathies developed in 5 patients after GKS, with the most common involving cranial nerves II and III.

CONCLUSIONS:

Gamma Knife surgery offers a high rate of tumor control and a reasonable rate of endocrine remission in patients with Cushing's disease. The cessation of cortisol-lowering medications around the time of GKS appears to result in a more rapid rate of remission. Delayed hypopituitarism and endocrine recurrence develop in a minority of patients and underscore the need for long-term multidisciplinary follow-up.

J Neurosurg. 2008 Oct;109(4):751-9. doi: 10.3171/JNS/2008/109/10/0751.

Management of Cushing's disease: outcome in patients with microadenoma detected on pituitary magnetic resonance imaging.

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OBJECT:

Outcomes of therapy for Cushing's disease (CD) vary depending on different aspects of presentation and diagnostic studies. The authors designed this study to verify the remission rate and outcomes after transsphenoidal surgery (TSS) for patients with CD who had positive findings on MR imaging.

METHODS:

Patients who had presented with CD at the University of Virginia for initial treatment between July 1992 and December 2005 were retrospectively reviewed. The patients included in the study were considered to be optimal surgical candidates, defined as an adult (>18 years of age) with classic clinical features of CD, laboratory studies confirming a central (pituitary/hypothalamic) adrenocorticotrophic hormone-dependent source of disease, and an MR imaging study revealing a microadenoma in the sella turcica.

RESULTS:

A total of 167 patients fulfilled the criteria. Thirty were men (18%) and 137 were women (82%). The mean age was 42.3 years (range 18.2-77 years). All patients underwent TSS. Surgical remission was achieved in 148 patients (88.6%), which was correlated with the surgeon's intraoperative identification of an adenoma ($p=0.03$). Histopathological confirmation of an adrenocorticotrophic hormone-secreting adenoma strongly correlated with remission ($p=0.0001$). Three patients (1.8%) had postoperative cerebrospinal fluid leaks, and 1 patient had meningitis. Transient diabetes insipidus was diagnosed and treated in 10 patients (6%), whereas permanent diabetes insipidus occurred in 8 patients (4.8%). Panhypopituitarism followed the surgery in 14 patients (8.3%), 13 of whom underwent total hypophysectomy (9 initially and 4 with early reoperations), and in 1 of 10 patients who underwent subtotal hypophysectomy. Nineteen patients (12.8%) who were initially in remission developed recurrent CD after an average of 50 months. The mean follow-up for the 167 patients was 39 months (range 6-157 months). Gamma Knife surgery was the most common modality of radiotherapy used to treat 31 patients (18.5%) who did not achieve remission or later presented with recurrent disease. Bilateral adrenalectomies were performed in 10 patients in the series (6%), 2 of whom developed Nelson's syndrome. The overall posttreatment remission rate was 95.8%.

CONCLUSIONS:

Even in patients with ideal diagnostic criteria of CD, there remain a significant number of cases in which TSS alone is not adequate to assure long-lasting remission. A multidisciplinary approach is essential to the achievement of satisfactory overall remission rates.

J Neurooncol. 2008 Oct;90(1):117-24. doi: 10.1007/s11060-008-9641-2. Epub 2008 Jun 21.

Applications of radiotherapy and radiosurgery in the management of pediatric Cushing's disease: a review of the literature and our experience.

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Surgical extirpation of pituitary adenomas is considered the mainstay of therapy in pediatric patients with Cushing's disease. However, a small subset of patients will require adjuvant therapy either due to tumor invasiveness, or disease recurrence. Conventional radiation therapy (or radiotherapy) delivers ionizing radiation to control hormonally active cells in fractionated doses (spread out over time) in order to give normal cells time

to recover, while radiosurgery involves focusing a high dose of radiation structures in a single treatment session to the adenoma while generally sparing the normal gland and surrounding of any substantial amount of radiation. This paper reviews the effectiveness of radiation in the treatment of pediatric Cushing's disease.

J Neurosurg. 2007 Jun;106(6):976-7; discussion 977-9.

Gamma Knife surgery for Cushing disease.

Weiss MH, Couldwell WT.

Comment on Gamma Knife surgery for Cushing's disease. [J Neurosurg. 2007]

J Neurosurg. 2007 Jun;106(6):980-7.

Gamma Knife surgery for Cushing's disease.

Jagannathan J1, Sheehan JP, Pouratian N, Laws ER, Steiner L, Vance ML.

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OBJECT:

In this study the authors address the efficacy and safety of Gamma Knife surgery (GKS) in patients with adrenocorticotrophic hormone-secreting pituitary adenomas.

METHODS:

A review of data collected from a prospective GKS database between January 1990 and March 2005 was performed in patients with Cushing's disease. All but one patient underwent resection for a pituitary tumor, without achieving remission. Successful endocrine outcome after GKS was defined as a normal 24-hour urinary free cortisol (UFC) concentration posttreatment after a minimum of 1 year of follow up. Patient records were also evaluated for changes in tumor volume, development of new hormone deficiencies, visual acuity, cranial nerve neuropathies, and radiation-induced imaging changes. Ninety evaluable patients had undergone GKS, with a mean endocrine follow-up duration of 45 months (range 12-132 months). The mean dose, to the tumor margin was 23 Gy (median 25 Gy). Normal 24-hour UFC levels were achieved in 49 patients (54%), with an average time of 13 months after treatment (range 2-67 months). In the 49 patients in whom a tumor was visible on the planning magnetic resonance (MR) image, a decrease in tumor size occurred in 39 (80%), in seven patients there was to change in size, and tumor growth occurred in three patients. Ten patients (20%) experienced a relapse of Cushing's disease after initial remission; the mean time to recurrence was 27 months (range 6-60 months). Seven of these patients underwent repeated GKS, with three patients achieving a second remission. New hormone deficiencies developed in 20 patients (22%), with hypothyroidism being the most common endocrinopathy after GKS. Five patients experienced new visual deficits or third, fourth, or sixth cranial nerve deficits; two of these patients had undergone prior conventional fractionated radiation therapy, and four of them had received previous GKS. Radiation-induced changes were observed on MR images in three patients; one had symptoms attributable to these changes.

CONCLUSIONS:

Gamma Knife surgery is an effective treatment for persistent Cushing's disease. Adenomas with cavernous sinus invasion that are not amenable to resection are treatable with the Gamma Knife. A second GKS treatment appears to increase the risk of cranial nerve damage. These results demonstrate the value of combining two neurosurgical treatment modalities-microsurgical resection and GKS-in the management of pituitary adenomas.

Eur J Endocrinol. 2007 Jan;156(1):91-8.

Gamma knife radiosurgery is a successful adjunctive treatment in Cushing's disease.

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OBJECTIVE:

Though transsphenoidal surgery remains the first-line treatment of Cushing's disease, recurrence occurs frequently. Conventional radiotherapy and anticortisolic drugs both have adverse effects. Stereotactic radiosurgery needs to be evaluated more precisely. The aim of this study was to determine long-term hormonal effects and tolerance of gamma knife (GK) radiosurgery in Cushing's disease.

DESIGN:

Forty patients with Cushing's disease treated by GK were prospectively studied over a decade, with a mean follow-up of 54.7 months. Eleven of them were treated with GK as a primary treatment.

METHODS:

Radiosurgery was performed at the Department of Functional Neurosurgery of Marseille, France, using the Leksell Gamma Unit B and C models. Median margin dose was 29.5 Gy. Patients were considered in remission if they had normalized 24-h free urinary cortisol and suppression of plasma cortisol after low-dose dexamethasone suppression test.

RESULTS:

Seventeen patients (42.5%) were in remission after a mean of 22 months (range 12-48 months). The two groups did not differ in terms of initial hormonal levels. Target volume was significantly higher in uncured than in remission group (909.8 vs 443 mm³, P = 0.038). We found a significant difference between patients who were on or off anticortisol drugs at the time of GK (20 vs 48% patients in remission respectively, P = 0.02).

CONCLUSION:

With 42% of patients in remission after a median follow-up of 54 months, GK stereotactic radiosurgery, especially as an adjunctive treatment to surgery, may represent an alternative to other therapeutic options in view of their adverse effects.

J Neurosurg. 2005 Nov;103(5 Suppl):413-20.

Single-center experience with pediatric Cushing's disease.

Kanter AS1, Diallo AO, Jane JA Jr, Sheehan JP, Asthagiri AR, Oskouian RJ, Okonkwo DO, Sansur CA, Vance ML, Rogol AD, Laws ER Jr.

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OBJECT:

Despite ongoing advances in surgical and radiotherapeutic techniques, pediatric Cushing's disease remains a diagnostic and therapeutic challenge. The authors report on the results of a single-center retrospective review of 33 pediatric patients with Cushing's disease, providing details with respect to clinical presentation, diagnostic evaluation, therapeutic course, complications, and outcomes.

METHODS:

There were 17 female and 16 male patients whose mean age was 13 years (range 5-19 years) in whom a diagnosis of Cushing's disease was based on clinical and biochemical criteria. Typical symptoms included weight gain (91%), prepubertal growth delay (83%), round facies (61%), hirsutism (58%), headache (45%), abdominal striae (42%), acne (33%), amenorrhea (24%), and hypertension (24%). In 67% of the cases, preoperative magnetic resonance images revealed a pituitary lesion and in 82% of the cases the imaging studies effectively predicted lateralization. Inferior petrosal sinus sampling was performed in seven patients (21%), and in all of these cases lateralization was 100% reliable. Fifty-five percent underwent selective adenomectomies and 45% underwent subtotal hypophysectomies. Complications included one case of diabetes insipidus, one of persistent hypocortisolemia necessitating prolonged glucocorticoid replacement therapy, and one minor vascular injury that did not necessitate postoperative management modification or cause sequelae. There were no surgery-related deaths and no cases of postoperative cerebrospinal fluid leakage or meningitis. During a mean follow-up period of 44 months, clinical remission was ultimately achieved in 91% of patients: 76% after transsphenoidal surgery alone and an additional 15% after adjuvant radiosurgery and/or adrenalectomy following surgical failure. Three patients (12%) experienced disease recurrence and underwent a second surgical procedure at 18, 81, and 92 months, respectively; based on clinical and biochemical criteria a second remission was achieved in all. Three patients (9%) remain with persistent disease.

CONCLUSIONS:

Pediatric Cushing's disease is a rare condition, often requiring a multidisciplinary diagnostic and a multimodal therapeutic approach for successful long-term remission.

J Endocrinol Invest. 2004 Nov;27(10):954-6.

Pregnancy in Cushing's disease shortly after treatment by gamma-knife radiosurgery.

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Gamma-knife radiosurgery (GKR) is considered as a possible treatment for patients affected by unsuccessfully surgically treated pituitary adenoma or not suitable for surgery. The disadvantages of this technique seem to be the length of time to the onset of remission, which is known to be at least of 6 months, and the possible adverse effects. We report here a case of a 13-yr-old female patient with Cushing's disease (CD) due to ACTH-secreting pituitary adenoma. After a complete clinical remission obtained by a transsphenoidal surgery, at the age of 18, the patient had a recurrence of ACTH-dependent hypercortisolism, and a second transsphenoidal surgery was performed. In April 1999, a second recurrence of CD was diagnosed and the patient underwent GKR on a small

pituitary mass, on the left side of the sella. In June 1999 amenorrhoea appeared, and in August 1999 pregnancy occurred. Although during the pregnancy the disease activity was still high, the fetus's growth was normal and in February 2000 a normal male infant was delivered. The baby and the mother did not show any biochemical signs or clinical symptoms of hypo- or hypercortisolism. This case is interesting, since GKR exerted a very rapid effect and turned to be safe even if performed shortly before pregnancy. Moreover, in spite of the still high disease activity, the pregnancy had a normal course and the fetus did not have any cortisol secretion abnormalities.

J Intern Med. 2003 Apr;253(4):454-62.

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

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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.

Int J Radiat Oncol Biol Phys. 2002 Nov 1;54(3):839-41.

Stereotactic radiosurgery for patients with ACTH-producing pituitary adenomas after prior adrenalectomy.

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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.

Neurochirurgie. 2002 May;48(2-3 Pt 2):294-9.

Cushing's disease resulting from pituitary corticotrophic microadenoma. Treatment results from transsphenoidal microsurgery and gamma knife radiosurgery.

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Cushing's disease and its associated clinical syndrome reflect the effects of excess cortisol on the individual. The cause of Cushing's disease is ordinarily an ACTH-secreting benign pituitary adenoma. The diagnosis of Cushing's disease is established by sophisticated endocrine testing and comprehensive imaging studies. Because of the devastating effects of excess cortisol, therapy that provides prompt and effective normalization of serum cortisol is essential. Currently this goal is best achieved by transsphenoidal microsurgery. This paper reviews the clinical presentation, laboratory analysis, surgical management and outcome in patients with Cushing's disease.

J Neurosurg. 2002 Dec;97(5 Suppl):422-8.

Gamma knife radiosurgery in the treatment of Cushing disease: long-term results.

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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 GKS 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.

Neurochirurgie. 2002 May;48(2-3 Pt 2):281-4.

[Clinical recurrence of Cushing syndrome without evidence of tumor recurrence: radical hypophysectomy?].

[Article in French]

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Outcome following radiation therapy for hormonally-active Cushing adenoma is reported. Conventional radiation using 20 to 30 grays improved mass and hormone level in 30 to 80% of the patient. Gamma-knife radiosurgery was at least as effective. These results are discussed in this review.

J Neurosurg. 2000 Nov;93(5):738-42.

Radiosurgery for Cushing's disease after failed transsphenoidal surgery.

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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.

Wien Klin Wochenschr. 1997 Jan 31;109(2):47-52.

[Diagnosis and therapy of Cushing syndrome].

[Article in German]

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Current diagnostic and therapeutic options in Cushing's syndrome have been retrospectively evaluated on the basis of 40 case histories of the years 1980 to 1994. After biochemical diagnosis, several radiological methods such as ¹³¹I-cholesterol-scintigraphy and, in 1 case, selective petrosal sinus blood sampling were employed. Out of 25 patients with central Cushing's syndrome 18 were cured by transsphenoidal pituitary surgery, in 1 case in combination with "Gamma-Knife" therapy. One patient was primarily treated by bilateral adrenalectomy, 5 as second intervention following unsuccessful pituitary surgery. One patient is not fully cured at present. Adrenal cortisol-producing adenomas were successfully treated by unilateral, subtotal or bilateral adrenalectomy in 9, 1 and 2 patients, respectively. Another patient with bilateral adrenal adenomas was treated medically following unilateral adrenalectomy. One patient with a cortisol-producing adrenal carcinoma died shortly after operation. One patient with an ACTH-producing pancreatic islet cell tumor died 1 year after initial remission. Adrenalectomy is the logical therapy in adrenal cortisol-producing adenomas. Improved diagnostic and surgical techniques have reduced bilateral adrenalectomy in patients with central Cushing's syndrome to rare cases in which transsphenoidal surgery (71% success rate) is the therapy of choice.

Surg Neurol. 1995 Feb;43(2):170-5; discussion 175-6.

Gamma knife surgery for Cushing's disease.

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1Department of Neurosurgery, Nakamura Memorial Hospital, Sapporo, Japan.

BACKGROUND:

The efficacy of gamma knife surgery on Cushing's disease is not well known to date. In most reported cases of Cushing's disease treated with gamma knife, the area to be irradiated was determined with computed tomography or pneumoencephalography. We report two cases of recurrent pituitary-dependent Cushing's disease treated with gamma knife using stereotactic magnetic resonance imaging (MRI).

MATERIALS AND METHODS:

Recurrent microadenomas were visualized as hypointense areas using gadolinium-enhanced MRI after two transsphenoidal surgeries in both cases. The doses of irradiation given were 35 Gy and 20 Gy to the margin of the tumors, and less than 8 Gy and 21 Gy to the optic apparatus and cranial nerves in the cavernous sinus, respectively.

RESULTS:

Both patients had clinical remission with normal serum cortisol and adrenocorticotrophic hormone levels, during 2-year follow-up after radiosurgery, without endocrinologic deficiency or neurologic deterioration.

CONCLUSIONS:

Gamma knife surgery can be an alternative therapy for Cushing's disease when pituitary adenomas are apart from the optic apparatus and can be visualized clearly by MRI, even if tumors are recurrent after microsurgery.

Acta Neurochir Suppl. 1994;62:39-42.

Tumour volume reduction following gamma knife radiosurgery: the relationship between X-ray and histological findings.

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The case histories of two young ladies with Cushing's disease are described. Both patients were treated first with Gamma Knife radiosurgery and subsequently by microsurgery. The radiosurgery caused a marked reduction in tumour volume but only a partial relief of the endocrinopathy. Comparison of the histological findings with the radiological findings following radiosurgery indicates that confluent necrosis is not a prerequisite for a reduction in tumour volume. It seems more likely that the reduction in tumour volume is related to changes in cellular dynamics.

Acta Paediatr Scand. 1986 May;75(3):388-95.

Treatment of Cushing's disease in childhood and adolescence by stereotactic pituitary irradiation.

Thorén M, Råhn T, Hallengren B, Kaad PH, Nilsson KO, Ravn H, Ritzén M, Petersen KE, Aarskog D.

Abstract

Eight children with Cushing's disease aged 6-18 years were treated with external radiation to the pituitary gland using ⁶⁰Co gamma radiation given with stereotactic technique. The dose given varied between 50 and 70 Gy. The observation time was 2.6 to 6.75 years. Seven children had a clinical remission with normal urinary cortisol excretion. One child had insufficient effect of two irradiations and underwent bilateral adrenalectomy. In the patients in remission the growth velocity increased during the first year after treatment but growth retardation occurred again during the second year. Insufficient growth hormone secretion was demonstrated in all subjects. Two patients were given thyroxine substitution and three showed evidence for secondary hypogonadism. In conclusion, stereotactic pituitary irradiation was effective in normalizing the excessive glucocorticoid production in children with Cushing's disease. However, with the doses used, it was not possible to maintain a normal anterior pituitary function.

Acta Endocrinol (Copenh). 1986 Jul;112(3):310-4.

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

Degerblad M, Råhn T, Bergstrand G, Thorén M.

Gamma radiation from ⁶⁰Co 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.

Arch Otorhinolaryngol. 1983;238(3):209-15.

Gamma irradiation effects on human ACTH-producing pituitary tumors in organ culture.

Rähn T, Thorén M, Anniko M.

Morphology (studied by light and electron microscopy) and hormone secretion were followed in organ cultures of adrenocorticotrophic hormone (ACTH)-secreting hormones after in vitro irradiation with a single dose of 70 Gy. The increase in ACTH secretion immediately after exposure was interpreted as an irradiation-induced direct effect on cell membrane permeability. The low secretory capacity for 120 h after irradiation is probably caused by an impairment of cell metabolism. Cell morphology slightly deteriorated 24-48 h after exposure. Later, cell morphology was restored and specimens investigated 5 days after irradiation showed normal morphology. It is concluded, that the fluctuations in serum ACTH in patients with Cushing's disease treated by stereotactic radiosurgery are caused by changes in the tumor cells proper rather than being due to hypothalamic influence.

Acta Endocrinol (Copenh). 1978 May;88(1):7-17.

Treatment of pituitary dependent Cushing's syndrome with closed stereotactic radiosurgery by means of ⁶⁰Co gamma radiation.

Thorén M, Rähn T, Hall K, Backlund EO.

Four patients with pituitary dependent Cushing's syndrome were treated with external irradiation to the pituitary using ⁶⁰Co gamma irradiation given with a stereotactic technique. The size of the sella turcica was normal or slightly enlarged in all patients. The doses given varied between 7000 and 10 000 rad, and the observation time ranged between 14 and 20 months. Three of the patients showed complete clinical remission and one marked improvement. One patient developed ACTH insufficiency, while none developed insufficient secretion of other pituitary hormones. No complications of the irradiation were observed.

NOTNLM. 19801201.1980;Epub

Stereotactic Radiosurgery In The Treatment Of Mb Cushing

Rahn, Thoren, Hall and Backlund

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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).

Surg Neurol. 1980 Aug;14(2):85-92.

Stereotactic radiosurgery in Cushing's syndrome: acute radiation effects.

Rähn T, Thorén M, Hall K, Backlund EO.

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.

Nelson's Syndrome

J Neurosurg. 2013 Dec;119(6):1493-7. doi: 10.3171/2013.7.JNS13389. Epub 2013 Aug 16.

Effect of stereotactic radiosurgery before bilateral adrenalectomy for Cushing's disease on the incidence of Nelson's syndrome.

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OBJECT:

Nelson's syndrome (NS) is a significant and frequent risk for patients with Cushing's disease (CD) who undergo bilateral adrenalectomy. A recent study has shown tumor progression in 47% of patients at risk for NS. The authors sought to define the rate of NS in patients who were treated with Gamma Knife stereotactic radiosurgery (GK SRS) prior to bilateral adrenalectomy.

METHODS:

Consecutive patients with CD who were treated with GK SRS after pituitary surgery but before bilateral adrenalectomy were included. Serial MRI sequences were analyzed to evaluate for pituitary tumor growth. Clinical evaluations were performed to screen for NS. Follow-up for adrenocorticotrophic hormone levels and hormone studies of other pituitary axes was performed.

RESULTS:

Twenty consecutive patients were followed with neuroimaging and clinically for a median of 5.4 years (range 0.6-12 years). One patient (5%) developed pituitary tumor growth consistent with NS 9 months after adrenalectomy. By Kaplan-Meier analysis, progression-free survival was 94.7% at 1, 3, and 7 years. No predisposing factors were identified for the tumor progression. Two patients developed new pituitary dysfunction and no patient developed cranial neuropathy or visual deficit after GK SRS.

CONCLUSIONS:

These findings suggest that GK SRS not only serves a role as second-line therapy for CD, but that it also provides prophylaxis for NS when used before bilateral adrenalectomy.

Eur J Endocrinol. 2009 Feb;160(2):143-8. Epub 2008 Nov 7.

Gamma knife stereotactic radiosurgery of Nelson syndrome.

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OBJECTIVE:

Gamma knife radiosurgery (GKR) can be used as primary or adjuvant therapy for the treatment of an ACTH-producing pituitary tumor after bilateral adrenalectomy, called Nelson syndrome (NS). We have examined the effect of GKR on tumor growth and ACTH-hypersecretion, and characterized the adverse events of this treatment in patients with NS.

DESIGN:

Cross-sectional follow-up study. First, retrospective data pre- and post-GKR were collected. Patients then underwent a predefined survey including radiological, endocrinological, ophthalmological, and neurosurgical evaluation.

SUBJECTS:

Ten patients treated with GKR for NS after previous bilateral adrenalectomy. The mean follow-up was 7 years. No patient was lost to follow-up.

RESULTS:

Tumor growth was stopped in all patients. The ACTH levels declined in eight patients, and normalized in one patient. There was a significant drop in ACTH levels, with a half-time of 2.8 years. No patient developed visual field defects or any other cranial nerve dysfunction as a result of treatment. Four patients started hormone substitution therapy during the follow-up period. The substitution therapy of three pituitary axes present at GKR treatment could be stopped during the same period. One patient developed a glioblastoma in the left parieto-occipital region 14 years after GKR, far from the field of treatment. As the radiation level was below 1Gy to this area, it is unlikely that the GKR treatment itself induced the malignant tumor.

CONCLUSION:

In patients with NS, GKR is an effective adjuvant treatment, carrying relatively few adverse effects. Although the risk of developing a secondary neoplasia after GKR is present, it is probably extremely low.

Endocr Pract. 1999 May-Jun;5(3):129-32.

Nelson's syndrome due to an intracavernous corticotropin-secreting adenoma.

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OBJECTIVE:

To report the first case of Nelson's syndrome due to an ectopic intracranial corticotropin-secreting tumor arising entirely within the cavernous sinus.

METHODS:

We present a case report of Nelson's syndrome with clinical, laboratory, and radiologic features throughout a 25-year period.

RESULTS:

A 54-year-old woman had been treated for Cushing's disease with bilateral adrenalectomy in 1971. Subsequently, Nelson's syndrome developed, and she had severe generalized hyperpigmentation and substantially increased plasma corticotropin levels. In 1976, she underwent a transsphenoidal hypophysectomy. Postoperatively, despite the development of panhypopituitarism and diabetes insipidus, she remained hyperpigmented and had persistently increased plasma corticotropin levels. Throughout the years, efforts to identify the site of the corticotropin-secreting tumor were unsuccessful until 1988, when magnetic resonance imaging revealed a mass in the right cavernous sinus; subsequently, petrosal sinus cannulation corroborated the intracavernous source

of excess corticotropin. Cobalt-60 gamma knife radiotherapy in 1992 was followed by a clinical and hormonal response 4 1/2 years later.

CONCLUSION:

This report describes only the second reported case of an intracranial corticotropin-secreting tumor arising entirely within the cavernous sinus and the first such case associated with Nelson's syndrome. Although rare, the possibility of an ectopic intracranial or extracranial pituitary adenoma should be considered in patients with pituitary hypersecretion without clear-cut intrasellar abnormalities or those with no response to surgical resection of the pituitary gland.

Endocrinologist.1999;9(4):313-315. Epub

Pregnancy and lactation in Nelson's syndrome

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A 27-year-old woman with Nelson's syndrome conceived, without ovulation induction or any assisted reproductive techniques, shortly after gamma knife treatment. She had an uncomplicated term pregnancy and had adequate lactation to breast-feed her healthy infant son. Previously, the patient had recurrent pituitary-dependent Cushing's treated by transphenoidal adenomectomy on two occasions followed by bilateral adrenalectomy.

Clin Neurol Neurosurg. 1998 Mar;100(1):60-3.

Beneficial gamma-knife radiosurgery in a patient with Nelson's syndrome.

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A 50-year-old female patient with Cushing's disease had undergone transsphenoidal removal of the pituitary adenoma and conventional radiotherapy in 1988. Since no remission was achieved, she underwent bilateral adrenalectomy in May 1989. During out-patient follow-up, she developed signs and symptoms due to invasive Adrenocorticotrophic hormone (ACTH)-producing macroadenoma (Nelson's syndrome) in 1994. ACTH levels at that time were 3400 ng/l. Near-total surgical resection of a 2.0 x 2.5 pituitary tumour which slightly extended laterally into the cavernous sinus was achieved by subfrontal approach in June 1994. However, she rapidly developed a recurrence of her complaints, with a visual field defect inferior-nasal of the left eye, and a second operation was carried out in November 1994. Culture of the tumour's cells revealed significant inhibition of ACTH production by bromocriptine. Adjuvant treatment with this drug therefore was started in November 1994. Because of the rapid recurrence it was decided to treat her with gamma-knife radiosurgery. The dose that was given in January 1995 was 12 Gy to the border and 40 Gy into the centre of the tumour. During a follow-up of more than 2 years, no recurrence, but even a minor reduction of tumour mass was observed by magnetic resonance imaging (MRI). Plasma ACTH levels decreased gradually to levels between 200 and 400 ng/l, and ophthalmologic complaints disappeared. It is concluded that gamma-knife radiosurgery may be a good alternative for patients with Nelson's syndrome who have rapidly recurring disease.

Prolactinomas

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Gamma Knife radiosurgery for medically and surgically refractory prolactinomas: long-term results

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INTRODUCTION: Prolactinomas are the most common functioning pituitary adenomas. Dopamine agonists (DA) are generally very effective in treating prolactinomas by inducing tumor volume regression and endocrine remission. A minority of patients do not respond to DA or are intolerant because of side-effects. Microsurgical resection when possible is the next treatment option, but cavernous sinus, dural, or bone involvement may not allow for complete resection. **OBJECTIVE:** We reviewed the outcome of patients with medically and surgically refractory prolactinomas treated with Gamma Knife radiosurgery (GKRS) during a 22 years follow-up period. **METHODS:** We reviewed the patient database at the University of Virginia Gamma Knife center during a 25-year period (1989-2014), identifying 38 patients having neurosurgical, radiological and endocrine follow-up. **RESULTS:** Median age at GKRS treatment was 43 years. Median follow-up was 42.3 months (range 6-207.9). 55.3 % (n = 21) were taking a dopamine agonist at time of GKRS. 63.2 % (n = 24) had cavernous sinus tumor invasion. Endocrine remission (normal serum prolactin off of a dopamine agonist) was achieved in 50 % (n = 19). GKRS induced hypopituitarism occurred in 30.3 % (n = 10). Cavernous sinus involvement was shown to be a significant negative

prognosticator of endocrine remission. Taking a dopamine agonist drug at the time of GKRS showed a tendency to decrease the probability for endocrine remission. CONCLUSION: GKRS for refractory prolactinomas can lead to endocrine remission in many patients. Hypopituitarism is the most common side effect of GKRS.

Pituitary. 2013 Mar;16(1):68-75.

Gamma knife stereotactic radiosurgery for drug resistant or intolerant invasive prolactinomas.

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We evaluated the efficacy of Gamma knife stereotactic radiosurgery (GKSR) as an adjunctive management modality for patients with drug resistant or intolerant cavernous sinus invasive prolactinomas. Twenty-two patients with cavernous sinus invasive prolactinoma underwent GKSR between 1994 and 2009. Thirteen patients were dopamine agonist (DA) resistant. Six patients were intolerant to DA. Three patients chose GKSR as their initial treatment modality in hopes they might avoid life long suppression medication. The median tumor volume was 3.0 cm³ (range 0.3–11.6). The marginal tumor dose (median= 15 Gy, range 12–25 Gy) prescribed was based on the dose delivered to the optic apparatus. The median follow-up interval was 36 months (range, 12–185). Endocrine normalization was defined as a normal serum prolactin level off DA (cure) or on DA. Endocrine improvement was defined as a decreased but still elevated serum prolactin level. Endocrine deterioration was defined as an increased serum prolactin level. Endocrine normalization was achieved in six (27.3%) patients. Twelve (54.5%) patients had endocrine improvement. Four patients (18.2%) developed delayed increased prolactin. Imaging-defined local tumor control was achieved in 19 (86.4%) patients, 12 of whom had tumor regression. Three patients had a delayed tumor progression and required additional management. One patient developed a new pituitary axis deficiency after GKSR. Invasive prolactinomas continue to pose management challenges. GKSR is a non invasive adjunctive option that may reduce prolactin levels in patients who are resistant to or intolerant of suppression medication. In a minority of cases, patients may no longer require long term suppression therapy.

World Neurosurg. 2010 Jul;74(1):147-52.

Gamma knife radiosurgery for patients with prolactin-secreting pituitary adenomas.

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OBJECTIVE:

To evaluate the efficacy of stereotactic radiosurgery (SRS) for patients with prolactin (PRL)-secreting pituitary adenomas that were refractory to medical management.

METHODS:

Retrospective review of 22 patients treated with SRS from 1994 until 2006. All patients were either intolerant or their tumors were unresponsive to dopamine agonist therapy. Nine patients (41%) had undergone prior transsphenoidal surgery. The median serum PRL concentration before SRS was 88.4 ng/mL (range, 25-943). The median treatment volume was 2.2 cm³ (range, 0.4-29.0); the median margin radiation dose was 25 Gy (range, 16-30). The median endocrinologic follow-up was 60 months (range, 16-129).

RESULTS:

Tumor control after SRS was 100%. Serum PRL concentration was significantly lower (median, 28.4 ng/mL) ($P = 0.006$) at last follow-up, but the 4-year actuarial rate of biochemical remission off medications was only 17%. No tested variable was associated with biochemical remission off medications. Overall, four patients (18%) had biochemical remission off medications and clinical improvement, three patients (14%) had normal serum PRL concentrations and clinical improvement on dopamine agonist therapy, seven patients (32%) had improved symptoms off medications but continued to have elevated serum PRL levels, and eight patients (36%) continued to be symptomatic with elevated PRL levels either on ($n = 3$) or off ($n = 5$) dopamine agonist therapy. The incidence of new anterior pituitary deficits was 42% at 4 years.

CONCLUSIONS:

SRS was effective in controlling tumor growth for patients with PRL-secreting pituitary adenomas, and the majority of patients were clinically improved.

World Neurosurg.2010;74(1):103-4. Epub 2011/02/09

Radiosurgery: a useful first-line treatment of prolactinomas?

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Clin Endocrinol (Oxf). 2009 May;70(5):732-41. doi: 10.1111/j.1365-2265.2008.03384.x. Epub 2008 Aug 15.

Use of the Leksell gamma knife in the treatment of prolactinoma patients.

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OBJECTIVE:

Pharmacological treatment with dopaminergic agonists (DA) is the treatment of choice for prolactinomas. Surgical and radiation treatment is also indicated in certain situations. We describe our 12-year experience in treating prolactinomas with the Leksell gamma knife (LGK).

DESIGN:

We followed 35 prolactinoma patients (25.7% microprolactinomas, 74.3% macroprolactinomas) treated with LGK irradiation. The mean follow-up period was 75.5 months. Prior to LGK irradiation, patients were treated with DA and 10 of them (28.6%) underwent neurosurgery. Indications for LGK irradiation were: DA intolerance (31.4%), DA resistance (45.7%) and efforts to reduce the DA dose or shorten the period of administration (22.9%). Pituitary function was monitored regularly at 6-month intervals. The central radiation dose range was 40-80 Gy (median 70 Gy), and the minimal peripheral dose was 20-49 Gy (median 34 Gy).

RESULTS:

Normoprolactinaemia was achieved in 37.1% of the patients who discontinued DA and in 42.9% of patients who continued DA treatment after LGK irradiation. The median time to prolactin normalization after discontinuation of DA was 96 months. No relapse was seen in any patient. After LGK irradiation, the prolactinoma stopped growing or decreased in size in all but one patient (97.1%).

CONCLUSION:

LGK treatment resulted in normoprolactinaemia in 80.0% of the patients, all of whom had failed pharmacological treatment due to DA resistance or intolerance. After achieving normoprolactinaemia, no relapse of hyperprolactinaemia was observed in any patient. The size of the adenoma decreased even in those patients in whom it was not changed by previous DA treatment.

Minerva Endocrinol. 2007 Sep;32(3):231-6.

Evolution of a prolactin-secreting pituitary microadenoma into a fatal carcinoma: a case report.

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Pituitary carcinomas are very rare tumors, nearly always presenting as widely invasive masses, although the hallmark of these lesions is the finding of distant metastases. One third of reported cases are prolactin (PRL)-secreting tumors. We report the case of a fatal pituitary carcinoma evolving within 4 years from a PRL-secreting microadenoma. A 22-year-old woman presented because of galactorrhea. Evaluation of the patient disclosed slight hyperprolactinemia and magnetic resonance imaging (MRI) showed a 7-mm intrapituitary lesion, which responded to treatment with cabergoline. About 4 years after the first evaluation she developed sudden headache, ptosis, and diplopia in the right eye. MRI disclosed the growth of a large pituitary mass, invading the right cavernous sinus. Despite two trans-sphenoidal surgical procedures followed by gamma-knife radiosurgery, the patient showed rapid local progression of the tumor and the occurrence of new lung lesions, probably of metastatic nature. The patient died 7 months after the development of her first neurological symptoms because of tumor apoplexy and subsequent subarachnoid hemorrhage. This case represents the first documented rapid evolution from a microprolactinoma initially responding to dopamine agonists to a fatal pituitary carcinoma.

Neurosurgery. 2006 Aug;59(2):255-66; discussion 255-66.

Gamma knife radiosurgery for medically and surgically refractory prolactinomas.

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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 cm³ (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 cm³ and who are not receiving dopamine agonist at the time of treatment will likely benefit most.

Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2006 Oct;31(5):714-6.

[Gamma knife treatment for pituitary prolactinomas].

[Article in Chinese]

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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.

Neurosurgery.2006;59(2):265-266. Epub

Gamma knife radiosurgery for medically and surgically refractory prolactinomas: Commentary

Goodkin, R., R. Goodkin, Seattle, WA, United States.

Endocrinologist.2001;11(1):61-67. Epub

A Fatal Malignant Macroprolactinoma in a Female Patient: Case Report and Review of the Literature

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Prolactinomas, the most common type of pituitary tumor, are prevalent in women. Macroprolactinomas, which often present with misleading and polymorphic symptoms, occur mainly in men. We review the literature on pituitary prolactinomas in women, and include a case-report of a 27 year old woman who underwent radical trans-sphenoidal excision of a large invasive macroprolactinoma. Postoperative evaluation of pituitary function showed normal PRL levels associated to hypopituitarism. Three years later, PRL levels increased associated with gross visual defects and a second operation with radiotherapy was done. Bromocriptine normalized PRL levels, and no recurrence was seen on CT/MRI for seven years. When she was 37 years old, the patient became resistant to dopamine-agonists, and the adenoma recurred with invasion of the cavernous sinus and a left frontal mass. Surgical removal of the frontal PRL-secreting metastasis reduced PRL levels to normal associated with quinagolide treatment. Two years later, a progressive increase in PRL levels heralded further expansion of the pituitary mass. The patient underwent a surgical debulking procedure followed by gamma-knife radiosurgery. Two months later, sudden rhinorrhea and visual loss occurred followed by coma. New growth of the pituitary neoplasm was evident. Three months later she died of thromboembolic events. Various causes of resistance to dopamine agonists are known. We suggest that the sudden loss of sensitivity to chronic dopamine-agonist treatment is a sign of the malignant transformation of a macroprolactinoma.

J Neurosurg. 2000 Dec;93 Suppl 3:10-3.

Gamma knife radiosurgery as a primary treatment for prolactinomas.

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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 (≥ 30 Gy) seemed to be associated with a better clinical outcome. Gamma knife radiosurgery may make prolactinomas more sensitive to the bromocriptine.

J Neurosurg. 2000 Dec;93 Suppl 3:14-8.

Gamma knife radiosurgery for prolactinomas.

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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.

Surg Neurol. 2000 Mar;53(3):267-74.

Telomerase activity and the expression of telomerase components in pituitary adenoma with malignant transformation.

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BACKGROUND:

Telomerase activity responsible for cellular immortality may participate the development of human cancers. Telomerase is a multisubunit ribonucleoprotein composed of at least three components: hTERT, hTERC, and

TEP1. This is the first report showing telomerase activity and telomerase component expression in pituitary adenoma with histological malignant transformation.

DESCRIPTION:

A 16-year-old male with a prolactin-producing pituitary adenoma with metastasis is presented. The patient underwent three partial resections of an intra- and suprasellar lesion over a 2-year period and received focal irradiation. Eight years after the first admission, a metastatic lesion to the subarachnoid space around the medulla oblongata was detected and the lesion was resected as the fourth operation. Furthermore, the suprasellar lesion showed regrowth and partial resection was performed as the fifth operation. The last two specimens were diagnosed as pituitary carcinoma. Radiotherapy with gamma knife was performed for the residual suprasellar lesion and a new lesion in the left temporal lobe after the fifth operation. Telomerase activity was examined by TRAP/TRAP-HPA methods, qualitatively and quantitatively. Telomere length was examined by Southern blot analysis, and the expression of telomerase components (hTERT, hTERC, and TEP1) was examined by reverse transcriptase-polymerase chain reaction (RT-PCR). The MIB1 index, telomerase activity, and hTERT expression increased according to histologic malignancy chronologically in this patient. None of the specimens showed immunoreactivity for p53, EGFR, or bc12. No telomerase activity was detected in pituitary adenomas without malignant transformation, other benign brain tumors, or normal brain tissues.

CONCLUSION:

We report a patient with pituitary adenoma transforming to carcinoma. The tumor cells acquired immortality and revealed malignant transformation during the course of the disease, that was proved by an increase of telomerase activity and hTERT expression.

Non Secreting

Journal of Neurosurgery.2016;125(1):202-12.Epub 2015/10/31

Early versus late Gamma Knife radiosurgery following transsphenoidal resection for nonfunctioning pituitary macroadenomas: a matched cohort study

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OBJECT Gamma Knife radiosurgery (GKRS) is frequently employed to treat residual or recurrent nonfunctioning pituitary macroadenomas. There is no consensus as to whether GKRS should be used early after surgery or if radiosurgery should be withheld until there is evidence of radiographic progression of tumor. **METHODS** This is a retrospective review of patients with nonfunctioning pituitary macroadenomas who underwent transsphenoidal surgery followed by GKRS between 1996 and 2013 at the University of Virginia Health System. Patients were stratified based on the interval between resection and radiosurgery. Operative results and imaging and clinical outcomes were compared across groups following early (≤ 6 months) or late (> 6 months) radiosurgery. **RESULTS** Sixty-four patients met the study criteria and were grouped based on early ($n = 32$) or late ($n = 32$) GKRS following transsphenoidal resection. There was a greater risk of tumor progression after GKRS in the late radiosurgical group ($p = 0.027$) over a median radiographic follow-up period of 68.5 months. Furthermore, there was a significantly higher occurrence of post-GKRS endocrinopathy in the late radiosurgical cohort ($p = 0.041$). Seventeen percent of patients without endocrinopathy in the early cohort developed new endocrinopathies during the follow-up period versus 64% in the late cohort ($p = 0.036$). This difference was primarily due to a significantly higher rate of tumor growth during the observation period of the late treatment cohort ($p = 0.014$). Of these patients with completely new endocrinopathies, radiation-associated pituitary insufficiency developed in 1 of 2 patients in the early group and in 3 of 7 (42.9%) patients in the late group. **CONCLUSIONS** Early treatment with GKRS appears to decrease the rate of radiographic and symptomatic progression of subtotaly resected nonfunctioning pituitary macroadenomas compared with late GKRS treatment after a period of expectant management. Delaying radiosurgery may place the patient at increased risk for adenoma progression and endocrinopathy.

Int J Radiat Oncol Biol Phys. 2014 Nov 15;90(4):903-10. Epub 2014 Sep 9.

Silent corticotroph adenomas after stereotactic radiosurgery: a case-control study.

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PURPOSE:

To investigate the safety and effectiveness of stereotactic radiosurgery (SRS) in patients with a silent corticotroph adenoma (SCA) compared with patients with other subtypes of non-adrenocorticotrophic hormone staining nonfunctioning pituitary adenoma (NFA).

METHODS AND MATERIALS:

The clinical features and outcomes of 104 NFA patients treated with SRS in our center between September 1994 and August 2012 were evaluated. Among them, 34 consecutive patients with a confirmatory SCA were identified. A control group of 70 patients with other subtypes of NFA were selected for review based on comparable baseline features, including sex, age at the time of SRS, tumor size, margin radiation dose to the tumor, and duration of follow-up.

RESULTS:

The median follow-up after SRS was 56 months (range, 6-200 months). No patients with an SCA developed Cushing disease during the follow-up. Tumor control was achieved in 21 of 34 patients (62%) in the SCA group, compared with 65 of 70 patients (93%) in the NFA group. The median progression-free survival (PFS) was 58 months in the SCA group. The actuarial PFS was 73%, 46%, and 31% in the SCA group and was 94%, 87%, and 87% in the NFA group at 3, 5, and 8 years, respectively. Silent corticotroph adenomas treated with a dose of ≥ 17 Gy exhibited improved PFS. New-onset loss of pituitary function developed in 10 patients (29%) in the SCA group, whereas it occurred in 18 patients (26%) in the NFA group. Eight patients (24%) in the SCA group experienced worsening of a visual field deficit or visual acuity attributed to the tumor progression, as did 6 patients (9%) in the NFA group.

CONCLUSION:

Silent corticotroph adenomas exhibited a more aggressive course with a higher progression rate than other subtypes of NFAs. Stereotactic radiosurgery is an important adjuvant treatment for control of tumor growth. Increased radiation dose may lead to improved tumor control in SCA patients.

Pituitary. 2014 Jun;17(3):227-31. doi: 10.1007/s11102-013-0494-0.

Peptide receptor radionuclide therapy in a patient with disabling non-functioning pituitary adenoma.

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Non-functioning pituitary adenoma (NFPA) with higher proliferation index (WHO II) are often a therapeutical challenge. Low somatostatin receptor expression in these tumors usually prevents a treatment with somatostatin analogs. In 1996, a 55-year-old patient was referred due to right-sided headache. A pituitary macroadenoma with infiltration into the right cavernous sinus was diagnosed. There was no visual field deficit and the clinical and biochemical work up was consistent with a NFPA. The patient underwent transsphenoidal surgery. Residual adenoma remained in the right cavernous sinus. Histologically, a null-cell adenoma with a high proliferation index was documented (MIB-1: 11.6%, WHO II). Somatostatin receptor autoradiography was performed in the surgical specimen showing a homogenous expression of sst2 receptors. Radiosurgery was completed with stable disease for 8 years. In 2004, the patient was diagnosed with an incomplete palsy of the right oculomotorius nerve and a significant increase in the volume of the adenoma in the right cavernous sinus. After a positive Octreoscan(®) the patient consented to an experimental therapy approach using Lutetium DOTATOC (3×200 mCi). The palsy of the oculomotorius nerve improved and remained stable until today (March 2013), the follow-up MRI scans demonstrated stable disease. This is the first case of a patient with a NFPA (WHO II) in whom PRRT successfully improved the local complications of the tumor for more than 8 years after ineffective surgery and gamma knife therapy. The determination of sst2 in vitro using autoradiography and in vivo by Octreoscan was instrumental to administer this therapy in a challenging situation.

J Neurosurg. 2014 Mar;120(3):645. doi: 10.3171/2013.10.JNS132248. Epub 2014 Jan 3.

Editorial: Gamma Knife radiosurgery and nonfunctioning pituitary adenomas.

Kovacs K1.

1Department of Laboratory Medicine, Division of Pathology, St. Michael's Hospital, Toronto, Ontario, Canada.

Comment in

Response. [J Neurosurg. 2014]

Comment on

Initial Gamma Knife radiosurgery for nonfunctioning pituitary adenomas. [J Neurosurg. 2014]

J Neurosurg. 2014 Mar;120(3):645. Epub 2014 Jan 3.

Editorial: Gamma Knife radiosurgery and nonfunctioning pituitary adenomas.

Kovacs K1.

1Department of Laboratory Medicine, Division of Pathology, St. Michael's Hospital, Toronto, Ontario, Canada.

Comment in

Response. [J Neurosurg. 2014]

Comment on

Initial Gamma Knife radiosurgery for nonfunctioning pituitary adenomas. [J Neurosurg. 2014]

J Neurosurg. 2014 Mar;120(3):647-54. Epub 2014 Jan 3.

Initial Gamma Knife radiosurgery for nonfunctioning pituitary adenomas.

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OBJECT:

Nonfunctioning pituitary adenomas (NFAs) are the most common type of pituitary adenoma and, when symptomatic, typically require surgical removal as an initial means of management. Gamma Knife radiosurgery (GKRS) is an alternative therapeutic strategy for patients whose comorbidities substantially increase the risks of resection. In this report, the authors evaluated the efficacy and safety of initial GKRS for NFAs.

METHODS:

An international group of three academic Gamma Knife centers retrospectively reviewed outcome data in 569 patients with NFAs.

RESULTS:

Forty-one patients (7.2%) underwent GKRS as primary management for their NFAs because of an advanced age, multiple comorbidities, or patient preference. The median age at the time of radiosurgery was 69 years. Thirty-seven percent of the patients had hypopituitarism before GKRS. Patients received a median tumor margin dose of 12 Gy (range 6.2-25.0 Gy) at a median isodose of 50%. The overall tumor control rate was 92.7%, and the actuarial tumor control rate was 94% and 85% at 5 and 10 years postradiosurgery, respectively. Three patients with tumor growth or symptom progression underwent resection at 3, 3, and 96 months after GKRS, respectively. New or worsened hypopituitarism developed in 10 patients (24%) at a median interval of 37 months after GKRS. One patient suffered new-onset cranial nerve palsy. No other radiosurgical complications were noted. Delayed hypopituitarism was observed more often in patients who had received a tumor margin dose > 18 Gy ($p = 0.038$) and a maximum dose > 36 Gy ($p = 0.025$).

CONCLUSIONS:

In this study, GKRS resulted in long-term control of NFAs in 85% of patients at 10 years. This experience suggests that GKRS provides long-term tumor control with an acceptable risk profile. This approach may be especially valuable in older patients, those with multiple comorbidities, and those who have endocrine-inactive tumors without visual compromise due to mass effect of the adenoma.

Eur J Endocrinol. 2013 Sep 14;169(4):487-95. doi: 10.1530/EJE-13-0400. Print 2013 Oct.

Gamma knife surgery for patients with volumetric classification of nonfunctioning pituitary adenomas: a systematic review and meta-analysis.

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OBJECTIVE:

The aim of this study was to scrutinize the literature to determine the efficacy and safety of gamma knife surgery (GKS) for the treatment of nonfunctioning pituitary adenomas (NFPAs) with volumetric classification.

METHODS:

Electronic databases including MedLine, PubMed, and Cochrane Central were searched. The literature related to patients with NFPAs treated with GKS was collected. Eligible studies reported on the rate of tumor control (RTC), the rate of radiosurgery-induced optic neuropathy injury (RRIONI), the rate of radiosurgery-induced endocrinological deficits (RRIED), and other parameters.

RESULTS:

A total of 17 studies met the criteria. based on the tumor volume, nfpas were divided into three groups: the RTC of group I (93 patients) with tumor volumes <2 ml was 99% (95% CI 96-100%), the RRIONI was 1% (95% CI 0-4%),

and the RRIED was 1% (95% CI 0-4%). The RTC of group II (301 patients) with volumes from 2 to 4 ml was 96% (95% CI 92-99%), the RRIONI was 0 (95% CI 0-2%), and RRIED was 7% (95% CI 2-14%). The RTC of group III (531 patients) with volumes larger than 4 ml was 91% (95% CI 89-94%), the RRIONI was 2% (95% CI 0-5%), and the RRIED was 22% (95% CI 14-31%). There were significant differences in the RTC and in the RRIED among the three groups ($P < 0.001$), indicating that there were higher RRIED and lower RTC with the increase of tumor volume.

CONCLUSIONS:

NFPAs, according to tumor volume classification, need stratification for GKS treatment. GKS is the optimal choice for the treatment of group II NFPAs. Patients with residual tumor volumes of < 4 ml will benefit most from GKS treatment.

J Neurosurg. 2013 Aug;119(2):446-56. doi: 10.3171/2013.3.JNS12766. Epub 2013 Apr 26.

Gamma Knife radiosurgery for the management of nonfunctioning pituitary adenomas: a multicenter study.

Sheehan JP1, Starke RM, Mathieu D, Young B, Sneed PK, Chiang VL, Lee JY, Kano H, Park KJ, Niranjan A, Kondziolka D, Barnett GH, Rush S, Golfinos JG, Lunsford LD.

1Department of Neurological Surgery, University of Virginia Health System, Charlottesville, VA, USA.

OBJECT:

Pituitary adenomas are fairly common intracranial neoplasms, and nonfunctioning ones constitute a large subgroup of these adenomas. Complete resection is often difficult and may pose undue risk to neurological and endocrine function. Stereotactic radiosurgery has come to play an important role in the management of patients with nonfunctioning pituitary adenomas. This study examines the outcomes after radiosurgery in a large, multicenter patient population.

METHODS:

Under the auspices of the North American Gamma Knife Consortium, 9 Gamma Knife surgery (GKS) centers retrospectively combined their outcome data obtained in 512 patients with nonfunctional pituitary adenomas. Prior resection was performed in 479 patients (93.6%) and prior fractionated external-beam radiotherapy was performed in 34 patients (6.6%). The median age at the time of radiosurgery was 53 years. Fifty-eight percent of patients had some degree of hypopituitarism prior to radiosurgery. Patients received a median dose of 16 Gy to the tumor margin. The median follow-up was 36 months (range 1-223 months).

RESULTS:

Overall tumor control was achieved in 93.4% of patients at last follow-up; actuarial tumor control was 98%, 95%, 91%, and 85% at 3, 5, 8, and 10 years postradiosurgery, respectively. Smaller adenoma volume (OR 1.08 [95% CI 1.02-1.13], $p = 0.006$) and absence of suprasellar extension (OR 2.10 [95% CI 0.96-4.61], $p = 0.064$) were associated with progression-free tumor survival. New or worsened hypopituitarism after radiosurgery was noted in 21% of patients, with thyroid and cortisol deficiencies reported as the most common postradiosurgery endocrinopathies. History of prior radiation therapy and greater tumor margin doses were predictive of new or worsening endocrinopathy after GKS. New or progressive cranial nerve deficits were noted in 9% of patients; 6.6% had worsening or new onset optic nerve dysfunction. In multivariate analysis, decreasing age, increasing volume, history of prior radiation therapy, and history of prior pituitary axis deficiency were predictive of new or worsening cranial nerve dysfunction. No patient died as a result of tumor progression. Favorable outcomes of tumor control and neurological preservation were reflected in a 4-point radiosurgical pituitary score.

CONCLUSIONS:

Gamma Knife surgery is an effective and well-tolerated management strategy for the vast majority of patients with recurrent or residual nonfunctional pituitary adenomas. Delayed hypopituitarism is the most common complication after radiosurgery. Neurological and cranial nerve function were preserved in more than 90% of patients after radiosurgery. The radiosurgical pituitary score may predict outcomes for future patients who undergo GKS for a nonfunctioning adenoma.

J Neurosurg. 2012 Dec;117 Suppl:84-8. doi: 10.3171/2012.6.GKS12986.

Low-dose Gamma Knife surgery for nonfunctioning pituitary adenomas.

El-Shehaby AM1, Reda WA, Tawadros SR, Abdel Karim KM.

1Gamma Knife Center Cairo, Nasser Institute, Shobra, Egypt.

OBJECT:

The primary concern when performing Gamma Knife surgery for pituitary adenoma is preservation of vision and pituitary function while achieving tumor growth control. Higher prescribed radiation doses are typically correlated with higher incidences of postradiosurgical hormone deficiencies. The goal of the present study was to retrospectively analyze the feasibility of using a lower prescribed radiation dose in the treatment of

nonfunctioning pituitary adenomas and the effect of this dose on vision, pituitary function, and tumor growth control.

METHODS:

The study was conducted in 38 patients with nonfunctioning pituitary adenomas, who were treated between January 2002 and July 2008. Twenty-one patients were available for follow-up (13 men and 8 women). The mean follow-up period was 44 months (range 24-90 months). Nineteen patients had previously undergone surgery. Pituitary dysfunction developed after surgery in 3 patients. One patient had an abnormal pituitary hormone profile before radiosurgery due to an attack of pituitary apoplexy. Visual field defects were present in 12 patients. The prescribed radiation dose was 12 Gy in all patients. The tumor volume ranged from 0.5 to 11.8 cm³ (mean 4.8 cm³). The maximum dose to the visual pathway was kept below 10 Gy. The mean maximum dose delivered to the visual pathway was 7.9 Gy.

RESULTS:

The patients were followed up for a period of 24 to 90 months (mean 44 months). The size of the tumor decreased in 11 patients (52%) and remained stable in 9 patients (43%). In 1 patient there was tumor growth outside the previous radiation field (on the contralateral side). Among the 12 patients with visual field defects, 9 (75%) experienced an improvement and the remaining patients' vision remained stable. In only 4 patients was the visual improvement associated with tumor shrinkage. The hormone profile remained normal in all patients except for the 4 patients who had pituitary dysfunction before radiosurgery.

CONCLUSIONS:

The 12-Gy prescribed dose used in this study seems to be sufficient for producing tumor control while sparing the patient from radiation-induced pituitary dysfunction. In addition, visual improvement was reported in a number of cases. A larger series and longer follow-up are required to confirm these results.

Neurosurgery. 2011 Dec;69(6):1188-99. doi: 10.1227/NEU.0b013e318222afed.

Long-term outcomes after gamma knife stereotactic radiosurgery for nonfunctional pituitary adenomas.

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BACKGROUND:

Nonfunctional pituitary adenomas (NFPAs) represent approximately 50% of all pituitary tumors.

OBJECTIVE:

To evaluate the long-term outcomes of stereotactic radiosurgery for NFPAs.

METHODS:

We evaluated the management outcomes of Gamma Knife radiosurgery in 125 patients with NFPAs over an interval of 22 years. The median patient age was 54 years (range, 16-88 years). One hundred ten patients (88%) had residual or recurrent tumors after ≥ 1 surgical procedures, and 17 (14%) had undergone prior fractionated radiation therapy. The median target volume was 3.5 cm³ (range, 0.4-28.1 cm³), and the median tumor margin dose was 13.0 Gy (range, 10-25 Gy).

RESULTS:

Tumor volume decreased in 66 patients (53%), remained stable in 46 (37%), and increased in 13 (10.4%) during a median of 62 months (maximum, 19 years) of imaging follow-up. The actuarial tumor control rates at 1, 5, and 10 years were 99%, 94%, and 76%, respectively. Factors associated with a reduced progression-free survival included larger tumor volume (≥ 4.5 cm³) and ≥ 2 prior recurrences. Of 88 patients with residual pituitary function, 21 (24%) suffered new hormonal deficits at a median of 24 months (range, 3-114 months). Prior radiation therapy increased the risk of developing new pituitary hormonal deficits. One patient (0.8%) had a decline in visual function, and 2 (1.6%) developed new cranial neuropathies without tumor progression.

CONCLUSION:

Stereotactic radiosurgery can provide effective management for patients with newly diagnosed NFPAs and for those after prior resection and/or radiation therapy.

Neurosurgery. 2011 Aug;69(2):284-93. doi: 10.1227/NEU.0b013e31821bc44e.

Long-term outcomes after Gamma Knife radiosurgery for patients with a nonfunctioning pituitary adenoma.

Gopalan R1, Schlesinger D, Vance ML, Laws E, Sheehan J.

1Department of Neurological Surgery, University of Virginia, Charlottesville, Virginia, USA.

BACKGROUND:

Nonfunctioning pituitary adenomas recur after microsurgery. Gamma Knife radiosurgery (GKRS) has been used to treat recurrent adenomas.

OBJECTIVE:

To evaluate the long-term rates of tumor control and development of hypopituitarism in patients with nonfunctioning pituitary adenomas after GKRS.

METHODS:

Forty-eight patients with a nonfunctioning pituitary adenoma treated between 1991 and 2004 at the University of Virginia were studied. All patients had more than 4 years of clinical and imaging follow-up.

RESULTS:

All patients underwent follow-up imaging and endocrine evaluations, with a duration ranging from 50 to 215 months (median, 80.5 months) and 57 to 201 months (median, 95 months), respectively. New hormone deficiency after GKRS occurred in 19 of 48 patients (39%). Corticotropin/cortisol deficiency developed in 8% of patients, thyroid hormone deficiency in 20.8%, gonadotropin deficiency in 4.2%, growth hormone/insulin-like growth factor 1 in 16.7%, and diabetes insipidus in 2%. Panhypopituitarism including diabetes insipidus developed in 1 patient. Overall, control of tumor volume was 83%. Tumor volume decreased in 36 patients (75%), increased in 8 patients (17%), and was unchanged in 4 patients (8%). Tumor volumes greater than 5 mL at the time of GKRS were associated with a significantly greater rate of growth ($P = .003$) compared with an adenoma with a volume of 5 mL or less.

CONCLUSION:

GKRS resulted in a high and durable rate of tumor control in patients with a nonfunctioning pituitary adenoma. A higher preoperative tumor volume was associated with an increased rate of tumor growth.

Neurosurgery. 2011 Aug;69(2):284-93. doi: 10.1227/NEU.0b013e31821bc44e.

Long-term outcomes after Gamma Knife radiosurgery for patients with a nonfunctioning pituitary adenoma.

Gopalan R1, Schlesinger D, Vance ML, Laws E, Sheehan J.

1Department of Neurological Surgery, University of Virginia, Charlottesville, Virginia, USA.

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CONCLUSION:

GKRS resulted in a high and durable rate of tumor control in patients with a nonfunctioning pituitary adenoma. A higher preoperative tumor volume was associated with an increased rate of tumor growth.

J Neuroophthalmol. 2009 Jun;29(2):136-9. doi: 10.1097/WNO.0b013e3181a57d19.

Ocular neuromyotonia after gamma knife stereotactic radiation therapy.

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Three patients who underwent multiple intracranial operations for recurrent nonsecreting pituitary adenomas followed by gamma knife stereotactic radiosurgery developed diplopia at 1, 5, and 6 years after the treatments. Examination disclosed features of ocular neuromyotonia, a phenomenon attributed to radiation damage to

ocular motor cranial nerves. Amply reported after external beam radiotherapy, neuromyotonia has not been described after radiosurgery previously. These patients are, however, exceptional in that all had undergone multiple sellar region operations or received high doses of radiotherapy, or both.

Pituitary. 2009;12(3):211-6. doi: 10.1007/s11102-008-0163-x.

Adjuvant Gamma Knife radiosurgery in non-functioning pituitary adenomas; low risk of long-term complications in selected patients.

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Complete surgical removal of non-functioning pituitary adenomas is often not possible. This retrospective study aimed at evaluating the long-term outcome and complications of Gamma Knife (GK) radiosurgery adjuvant to pituitary microsurgery in selected patients with small tumour remnants treated 1994-2004. Thirteen men and ten women, median age 49 years, were identified. Prior to GK 15 patients had remaining pituitary function. Median size of the tumours was 1.1 cm³. Median marginal dose was 20 Gy. Median follow-up with MR imaging was 78 and 97 months for clinical evaluation. Tumour growth control was 100%, irrespectively of growth hormone (GH) therapy for 72 months (n = 10). Only one recurrence was discovered outside radiation field and no new hypopituitarism was developed. This report suggests that in well-selected patients the long-term risk of complications is low and with careful surveillance GH insufficiency can be replaced. Lifelong follow-up is mandatory.

Int J Radiat Oncol Biol Phys. 2008 Apr 1;70(5):1325-9. Epub 2007 Oct 29.

Gamma knife radiosurgery for patients with nonfunctioning pituitary adenomas: results from a 15-year experience.

Pollock BE1, Cochran J, Natt N, Brown PD, Erickson D, Link MJ, Garces YI, Foote RL, Stafford SL, Schomberg PJ.

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PURPOSE:

To evaluate the efficacy and complications of stereotactic radiosurgery for patients with nonfunctioning pituitary adenomas (NFA).

METHODS AND MATERIALS:

This was a retrospective review of 62 patients with NFA undergoing radiosurgery between 1992 and 2004, of whom 59 (95%) underwent prior tumor resection. The median treatment volume was 4.0 cm³ (range, 0.8-12.9). The median treatment dose to the tumor margin was 16 Gy (range, 11-20). The median maximum point dose to the optic apparatus was 9.5 Gy (range, 5.0-12.6). The median follow-up period after radiosurgery was 64 months (range, 23-161).

RESULTS:

Tumor size decreased for 37 patients (60%) and remained unchanged for 23 patients (37%). Two patients (3%) had tumor growth outside the prescribed treatment volume and required additional treatment (fractionated radiation therapy, n = 1; repeat radiosurgery, n = 1). Tumor growth control was 95% at 3 and 7 years after radiosurgery. Eleven (27%) of 41 patients with normal (n = 30) or partial (n = 11) anterior pituitary function before radiosurgery developed new deficits at a median of 24 months after radiosurgery. The risk of developing new anterior pituitary deficits at 5 years was 32%. The 5-year risk of developing new anterior pituitary deficits was 18% for patients with a tumor volume of < or = 4.0 cm³ compared with 58% for patients with a tumor volume >4.0 cm³ (risk ratio = 4.5; 95% confidence interval = 1.3-14.9, p = 0.02). No patient had a decline in visual function.

CONCLUSIONS:

Stereotactic radiosurgery is effective in the management of patients with residual or recurrent NFA, although longer follow-up is needed to evaluate long-term outcomes. The primary complication is hypopituitarism, and the risk of developing new anterior pituitary deficits correlates with the size of the irradiated tumor.

Acta Neurochir (Wien). 2007 Oct;149(10):999-1006; discussion 1006. Epub 2007 Aug 6.

Gamma knife radiosurgery for endocrine-inactive pituitary adenomas.

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BACKGROUND:

The goal of nonsecreting pituitary adenoma radiosurgery is to halt tumour growth and to maintain normal performance of the hypophysis and the functionally important structures around the sella. The effectiveness of gamma knife radiosurgery was evaluated.

METHOD:

Over a period of 10 years (1993-2003), 140 patients with nonsecreting pituitary adenoma were treated by Leksell gamma knife at our Centre. Seventy-nine of them were followed up for longer than 3 years. Their age range was 24-73 years, with a median of 54 years. Eighty-five percent of them had previous open surgery. Fifteen patients had adenoma contact with the optic tract. Fourteen patients had a normally functioning hypophysis, 48 patients had complete panhypopituitarism, while the rest retained partial functions of the normal hypophysis. Adenoma volumes ranged between 0.1 and 31.3, the median being 3.45 ccm. The marginal dose ranged between 12 and -35 Gy, with a median of 20 Gy.

FINDINGS:

The follow-up ranged from 36 to 122 months, with a median of 60 months. No adenoma growth was detected; 89% of treated adenomas decreased in size, with a median volume reduction of 61%. There was no perimeter vision impairment after radiosurgery, while 4 out of 52 patients with abnormal perimeter vision reported improvement. There was no impairment of oculomotor nerve function. Impairment of hypophysis function was observed in 2 patients.

CONCLUSIONS:

Radiosurgery has a reliable antiproliferative effect on nonsecreting pituitary adenomas. It is a safe treatment with a low risk of morbidity. Short contact between a nonsecreting pituitary adenoma and the optic pathway is not an absolute contraindication for Gamma knife radiosurgery.

J Neurosurg. 2006 Jun;104(6):876-83.

Gamma surgery in the treatment of nonsecretory pituitary macroadenoma.

Mingione V1, Yen CP, Vance ML, Steiner M, Sheehan J, Laws ER, Steiner L.

1Department of Neurological Surgery, Lars Leksell Center for Gamma Surgery, University of Virginia Health System, Charlottesville, Virginia 22908, USA.

OBJECT:

The authors report on a retrospective analysis of the imaging and clinical outcomes following gamma surgery in 100 patients with nonsecretory pituitary macroadenoma.

METHODS:

Between June 1989 and March 2004, 100 consecutive patients with nonsecretory pituitary macroadenoma were treated at the Lars Leksell Center for Gamma Surgery, University of Virginia Health System (Charlottesville, VA). Ninety-two patients had residual or recurrent macroadenoma following one or more surgical procedures. In eight patients, gamma surgery was the primary treatment. Ten patients received conventional fractionated radiotherapy before the gamma surgery. Sixty-nine patients required hormone replacement therapy for one or more deficits before gamma knife treatment. Peripheral doses between 5 and 25 Gy (mean 18.5 Gy) were administered. Imaging and endocrinological follow-up evaluations were performed in 90 patients; these studies ranged from 6 to 142 months (mean 44.9 months) and 6 to 127 months (mean 47.9 months), respectively. Tumor volume decreased in 59 patients (65.6%), remained unchanged in 24 (26.7%), and increased in seven (7.8%). The minimal effective peripheral dose was 12 Gy; peripheral doses greater than 20 Gy did not seem to provide additional benefit. Of 61 patients with a partially or fully functioning pituitary gland and follow-up data, 12 (19.7%) suffered new hormone deficits following gamma surgery. In patients with endocrinological follow-up data that had been collected over more than 2 years, the rate of new deficits was 25%. No neurological morbidity or death was related to treatment.

CONCLUSIONS:

Current experience suggests that gamma surgery is an appropriate means of managing recurrent or residual nonsecretory pituitary macroadenoma following microsurgery and a primary treatment in selected patients. To evaluate definite rates of recurrence and new endocrine deficiencies, long-term follow-up studies are needed.

Rivista Medica.2005;11(1-2):65-69. Epub

Role of Gamma Knife Radiosurgery in the treatment of residual non functioning pituitary adenomas

Picozzi, P., Mortini, P., Losa, M., Franzin, A., Attuati, L., Valle, M. A., Gioia,

L., Vimercati, A. and Giovanelli, M.,Dr. P. Picozzi, U.F. di Radiochirurgia Stereotassica, Dipartimento di Neurochirurgia, Via Olgettina 60, 20132, Milano, Italy e-mail: Dicozzi.Diero@hsr.it.

We studied the natural history of non functioning pituitary adenomas in a series of patients who had undergone partial surgical debulking in our Centre. When a residual adenomatous tissue was demonstrated on post-

operatory MRI, some of them were subjected to Gamma Knife Radiosurgery one year after the operation, whereas another group was followed with serial MR images and neuro-ophtalmologic evaluation. In our series GKRS has demonstrated to be effective in local tumor control and prevention of tumor recurrence.

J Neurosurg. 2005 Jan;102 Suppl:71-4.

Radiosurgery and the prevention of regrowth of incompletely removed nonfunctioning pituitary adenomas.

Picozzi P1, Losa M, Mortini P, Valle MA, Franzin A, Attuati L, Ferrari da Passano C, Giovanelli M.

1Pituitary Unit of the Department of Neurosurgery, Istituto Scientifico San Raffaele, Università Vita-Salute, Milano, Italy. picozzi.piero@hsr.it

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 cm³ to 1.6 +/- 0.2 cm³ 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.

No Shinkei Geka. 2005 Aug;33(8):777-83.

[The usefulness of adjuvant therapy using gamma knife radiosurgery for the recurrent or residual nonfunctioning pituitary adenomas].

[Article in Japanese]

Iwai Y1, Yamanaka K, Yoshioka K, Yoshimura M, Honda Y, Matsusaka Y, Komiyama M, Yasui T.

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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.

Neurosurgery. 2005 Apr;56(4):699-705; discussion 699-705.

Radiosurgery for nonfunctioning pituitary adenomas.

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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 cm³ (median, 2.5 cm³). 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.

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Gamma knife radiosurgery for nonfunctioning pituitary adenomas.

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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.

J Neurosurg. 2004 Mar;100(3):438-44.

Gamma knife surgery for treatment of residual nonfunctioning pituitary adenomas after surgical debulking.

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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 cm³ 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.

Neurosurgery. 2003 Nov;53(5):1086-91; discussion 1091-4.

Stereotactic radiosurgery as an alternative to fractionated radiotherapy for patients with recurrent or residual nonfunctioning pituitary adenomas.

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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.

J Neurosurg. 2002 Dec;97(5 Suppl):429-32.

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

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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.

J Neurosurg. 2002 Dec;97(5 Suppl):408-14.

Radiosurgery for residual or recurrent nonfunctioning pituitary adenoma.

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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.

Neuropathology. 2001 Dec;21(4):288-93.

A case of non-functioning pituitary adenoma with Cushing's syndrome upon recurrence.

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A 49-year-old woman presented with left visual disturbance. No signs of Cushing's disease were evident. Basal levels of serum cortisol and plasma adrenocorticotropic hormone (ACTH) were 16.8 microg/dL and 66.0 pg/mL, respectively. MRI demonstrated an irregularly shaped large pituitary tumor, and the patient then underwent transsphenoidal surgery. By light microscopy the tumor represented a chromophobic adenoma with a few of the adenoma cells showing immunoreactivity for ACTH. On the basis of clinical and light microscopic examinations, the diagnosis of silent corticotroph adenoma was made. Electron microscopy, however, demonstrated the honeycomb Golgi complex that has been reported as a typical finding of gonadotroph adenomas. MRI taken 7 months after the first operation revealed adenoma regrowth. Transcranial surgery was performed, and histology demonstrated a chromophobic pituitary adenoma with most cells immunopositive for ACTH. She was treated with gamma knife postoperatively. Three months later, MRI revealed remarkable shrinkage of the adenoma, but she developed typical signs and symptoms of Cushing's disease. Thus, the hormone immunostaining and biological activity of pituitary adenomas may change with time.

Risk/Prognostic Factors

J Neurosurg. 2012 Jun;116(6):1304-10. doi: 10.3171/2012.2.JNS111630. Epub 2012 Mar 16.

Cranial nerve dysfunction following Gamma Knife surgery for pituitary adenomas: long-term incidence and risk factors.

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Abstract

OBJECT:

Gamma Knife surgery (GKS) has become a significant component of neurosurgical treatment for recurrent secretory and nonsecretory pituitary adenomas. Although the long-term risks of visual dysfunction following microsurgical resection of pituitary adenomas has been well studied, the comparable risk following radiosurgery is not well defined. This study evaluates the long-term risks of ophthalmological dysfunction following GKS for recurrent pituitary adenomas.

METHODS:

An analysis of 217 patients with recurrent secretory (n = 131) and nonsecretory (n = 86) pituitary adenomas was performed to determine the incidence of and risk factors for subsequent development of visual dysfunction. Patients underwent ophthalmological evaluation as part of post-GKS follow-up to assess for new or worsened cranial nerve II, III, IV, or VI palsies. The median follow-up duration was 32 months. The median maximal dose was 50 Gy, and the median peripheral dose was 23 Gy. A univariate analysis was performed to assess for risk factors of visual dysfunction post-GKS.

RESULTS:

Nine patients (4%) developed new visual dysfunctions, and these occurred within 6 hours to 34 months following radiosurgery. None of these 9 patients had tumor growth on post-GKS neuroimaging studies. Three of these patients had permanent deficits whereas in 6 the deficits resolved. Five of the 9 patients had prior GKS or radiotherapy, which resulted in a significant increase in the incidence of cranial nerve dysfunction (p = 0.0008). An increased number of isocenters (7.1 vs 5.0, p = 0.048) was statistically related to the development of visual dysfunction. Maximal dose, margin dose, optic apparatus dose, tumor volume, cavernous sinus involvement, and suprasellar extension were not significantly related to visual dysfunction (p >0.05).

CONCLUSIONS:

Neurological and ophthalmological assessment in addition to routine neuroimaging and endocrinological follow-up are important to perform following GKS. Patients with a history of radiosurgery or radiation therapy are at higher risk of cranial nerve deficits. Also, a reduction in the number of isocenters delivered, along with volume treated, particularly in the patients with secretory tumors, appears to be the most reasonable strategy to minimize the risk to the visual system when treating recurrent pituitary adenomas with stereotactic radiosurgery.

J Neurosurg. 2011 Feb;114(2):303-9. doi: 10.3171/2010.5.JNS091635. Epub 2010 Jun 11.

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

Sheehan JP1, Pouratian N, Steiner L, Laws ER, Vance ML.

OBJECT:

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

METHODS:

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

RESULTS:

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

CONCLUSIONS:

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

J Neurooncol. 2009 Jun;93(2):263-7. doi: 10.1007/s11060-008-9766-3. Epub 2008 Dec 20.

Radiation-induced optic neuritis after pituitary adenoma radiosurgery in a patient with multiple sclerosis: case report.

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OBJECTIVE AND IMPORTANCE:

To describe a rare case of optic neuritis onset after Gamma Knife stereotactic radiosurgery.

CLINICAL PRESENTATION:

Nine years after transsphenoidal subtotal resection of a pituitary adenoma, this 43-year-old woman had elevated serum prolactin levels and headaches.

INTERVENTION:

Gamma Knife stereotactic radiosurgery to residual pituitary tumor.

CONCLUSION:

To our knowledge, this is the first report of radiation-induced optic neuritis after radiosurgery in a patient with multiple sclerosis.

Neurosurgery. 2007 Aug;61(2):270-80; discussion 280.

Pituitary adenomas treated with gamma knife radiosurgery: volumetric analysis of 100 cases with minimum 3 year follow-up.

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OBJECTIVE:

To analyze pituitary adenoma volume changes after gamma knife radiosurgery (GKRS) in patients with 3 years of follow-up and to investigate factors that might affect these changes.

METHODS:

Between January 1997 and March 2004, a total of 1930 patients were treated in the Gamma Knife Unit of the Marmara University Department of Neurosurgery in Istanbul, Turkey. Three hundred sixty of these patients had pituitary adenomas (PAs). This prospectively designed clinical study documents the radiological-volumetric analysis for the first 100 of these patients with PAs who had a minimum of 3 years of follow-up and met the study requirements. Each tumor was assessed with serial magnetic resonance imaging scans after radiosurgery; at each time point, adenoma volume was expressed as a percentage of the tumor's initial volume. Volume changes were investigated relative to margin dose, the cavernous sinus infiltration, and endocrinological type of adenoma.

RESULTS:

At the end of the first year after GKRS, the PA volumes had decreased to approximately 90% of the initial volume on average. The corresponding approximate averages for the ends of Years 2 and 3 were 80 and 70% of the initial volume, respectively. At 3 years after GKRS, the PAs in the group with a peripheral dose of less than 17 Gy were reduced to approximately 80% of the initial volume on average. In contrast, the tumors in the patients with marginal doses of 21 to 23 Gy were reduced to approximately 60% of the initial volume at this stage. The adenomas treated with the highest marginal doses (>27 Gy) showed the earliest volume decreases after GKRS (6-9 mo after the procedure). Cavernous sinus noninfiltrating adenomas showed greater volume decreases after GKRS; on average, these masses were reduced to approximately 50% of their initial volume at 3 years. In contrast, the PAs that had infiltrated the cavernous sinus had only dropped to approximately 80% of their initial volume at this stage. The growth hormone-secreting PAs showed the maximum volume decrease with GKRS. On average, these lesions were approximately 60% of their initial volume at the 3-year stage. The nonfunctioning tumors and the prolactin-secreting adenomas showed similar volume changes over time. On average, these tumors had dropped to approximately 75 and 70% of the initial volume, respectively, by 3 years after GKRS.

CONCLUSION:

Gamma knife radiosurgery halts the growth of pituitary adenomas. Cavernous sinus extension and margin dose are the most important determinants of adenoma volume after this type of therapy.

General/Other

Endocrine.2016;2016/10/01

Frequency, pattern, and outcome of recurrences after gamma knife radiosurgery for pituitary adenomas

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Gamma Knife radiosurgery is often used in pituitary adenomas. Aim of our study is to describe the characteristics and long-term outcome of patients with adenoma recurrence after Gamma Knife radiosurgery. We conducted a retrospective analysis of patients with pituitary adenoma treated by Gamma Knife radiosurgery between 1994 and 2014. Tumor recurrence was labeled as "in field" when the tumor growth occurred adjacent or within the prescribed isodose, whereas it was classified as "out of field" when the tumor growth occurred outside the prescribed isodose. Five hundred forty-three patients were included, 272 (50.1 %) had a nonfunctioning pituitary adenoma (NFPA) and 271 (49.9 %) patients had a hormone secreting-pituitary adenoma. The median follow-up after GKRS was 78 months (IQR, 36-125 months). Thirty-nine patients (7.2 %) had recurrence of disease and it was more frequent in patients with NFPA than in patients with hormone secreting adenomas (9.6 % vs. 4.8 %). The 10-yr progression-free survival in patients with NFPA was 78.7 % (95 % CI 69.5 - 87.9 %), as compared with 93.3 % (95 % CI 89.3 - 97.3 %; $p < 0.01$) in hormone secreting adenomas. Tumor recurrence was "in field" in 17 cases (43.6 %) and "out of field" in 22 cases (56.4 %). Seven of the 39 patients with recurrence died despite further treatments. Six of these patients had an "in field" recurrence. Recurrence of a pituitary adenoma after GKRS may occur several years after initial treatment. Distinction between "in field" and "out of field" tumor recurrence probably reflects two different pathophysiological mechanisms and may have prognostic importance.

Clinical Neurology and Neurosurgery.2016;150(139-142).Epub 2016/09/26

Fractionated Gamma Knife surgery for giant pituitary adenomas

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OBJECTIVE: To analyze the feasibility and effectiveness of fractionated Gamma Knife surgery (FGKS) for giant pituitary adenomas. **METHODS:** From June 2005 to May 2016, 14 patients with giant pituitary adenomas were treated with FGKS, and 10 patients (71%) completed follow-up evaluation. All patients had undergone surgical resection at least once prior to FGKS. The median-volume of the adenomas was 17.6cm³(range 4.9-61cm³). **RESULTS:** The median follow-up period was 31.5 months (range 6-58 months). The size of the tumors decreased in 6 patients and remained stable in 4 patients. The visual acuity improved in 1 patient. None of the patients suffered from vision deterioration caused by FGKS. **CONCLUSION:** FGKS is an effective treatment modality for giant pituitary adenomas in selected patients.

Acta Neurochirurgica.2016;158(9):1697-700.Epub 2016/07/21

Radiosurgery for infundibulum adenoma: stalk dose implications

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Treating pituitary adenomas in the infundibulum with stereotactic radiosurgery (SRS), achieving tumor volume control while preserving pituitary endocrine function and visual function, is challenging. We present a case of a recurrent remnant infundibular lesion treated with Gamma Knife surgery (GKS). The mass was treated with microsurgical resection twice, and the residual stalk lesion was treated with single-session SRS employing a margin dose of 15 Gy to the infundibulum. Five years after GKS, tumor regression persists without visual dysfunction or hypopituitarism. Radiosurgical doses of 30 Gy to the pituitary stalk may be tolerated by patients while maintaining endocrine function.

Curr Opin Endocrinol Diabetes Obes.2016;23(4):331-8.Epub 2016/06/25

Advances in Gamma Knife radiosurgery for pituitary tumors

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PURPOSE OF REVIEW: For the residual/recurrent pituitary adenomas, stereotactic radiosurgery (SRS) plays an important role in long-term tumor control and, for secretory adenomas, endocrine remission. The purpose of

this review is to address the advances in SRS technique and detail the latest treatment strategies for various types of pituitary adenomas with a focus on recently published literature. RECENT FINDINGS: From recent publications, SRS may be considered as an upfront treatment in patients with an adenoma that resides largely in the cavernous sinus and for whom resection is unlikely to produce substantial reduction in the overall tumor volume. Early treatment (<6 months after prior resection) with SRS appears to decrease the rate of tumor progression of subtotally resected nonfunctioning pituitary macroadenomas. Some types of adenomas may appear more aggressive with a high recurrence rate, for example, silent corticotroph pituitary adenomas, or sparsely granulated somatotroph-cell adenomas, may be indicated for a high-radiation dose. Finally, whole-sellar radiation and fractionated SRS are the alternative strategies, and may be indicated for challenging cases. SUMMARY: The role of SRS for the pituitary adenoma is well established, and the treatment strategy is increasingly individualized based upon tumor histology, location, and volume. Hypopituitarism is the most complicated and can occur even years after SRS.

World Neurosurg.2016;91(121-8).Epub 2016/04/10

Primary Endoscopic Transnasal Transsphenoidal Surgery for Giant Pituitary Adenoma

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OBJECTIVES: Giant pituitary adenoma (>4 cm) remains challenging because the optimal surgical approach is uncertain. METHODS: Consecutive patients with giant pituitary adenoma who underwent endoscopic transnasal transsphenoidal surgery (ETTS) as the first and primary treatment were retrospectively reviewed. Inclusion criteria were tumor diameter ≥ 4 cm in at least 1 direction, and tumor volume ≥ 10 cm³. Exclusion criteria were follow-ups <2 years and diseases other than pituitary adenoma. All the clinical and radiologic outcomes were evaluated. RESULTS: A total of 38 patients, average age 50.8 years, were analyzed with a mean follow-up of 72.9 months. All patients underwent ETTS as the first and primary treatment, and 8 (21.1%) had complete resection without any evidence of recurrence at the latest follow-up. Overall, mean tumor volume decreased from 29.7 to 3.2 cm³ after surgery. Residual and recurrent tumors (n = 30) were managed with 1 of the following: Gamma Knife radiosurgery (GKRS), reoperation (redo ETTS), both GKRS and ETTS, medication, conventional radiotherapy, or none. At last follow-up, most of the patients had favorable outcomes, including 8 (21.1%) who were cured and 29 (76.3%) who had a stable residual condition without progression. Only 1 (2.6%) had late recurrence at 66 months after GKRS. The overall progression-free rate was 97.4%, with few complications. CONCLUSIONS: In this series of giant pituitary adenoma, primary (ie, the first) ETTS yielded complete resection and cure in 21.1%. Along with adjuvant therapies, including GKRS, most patients (97.4%) were stable and free of disease progression. Therefore, primary ETTS appeared to be an effective surgical approach for giant pituitary adenoma.

Neurosurgery.2016;2016/03/11

Emerging Indications for Fractionated Gamma Knife Radiosurgery

McTyre, E., Helis, C. A., Farris, M., Wilkins, L., Sloan, D., Hinson, W. H., Bourland, J. D., Dezarn, W. A., Munley, M. T., Watabe, K., Xing, F., Laxton, A. W., Tatter, S. B. and Chan, M. D., *Department of Radiation Oncology, Wake Forest School of Medicine, Winston-Salem, North Carolina; double daggerDepartment of Cancer Biology, Wake Forest School of Medicine, Winston-Salem, North Carolina; section signDepartment of Neurosurgery, Wake Forest School of Medicine, Winston-Salem, North Carolina.

BACKGROUND: Gamma Knife radiosurgery (GKRS) allows for the treatment of intracranial tumors with a high degree of dose conformality and precision. There are, however, certain situations wherein the dose conformality of GKRS is desired, but single-session treatment is contraindicated. In these situations, a traditional pin-based GKRS head frame cannot be used, because it precludes fractionated treatment. OBJECTIVE: To report our experience in treating patients with fractionated GKRS using a relocatable, noninvasive immobilization system. METHODS: Patients were considered candidates for fractionated GKRS if they had 1 or more of the following

indications: a benign tumor >10 cc in volume or abutting the optic pathway, a vestibular schwannoma with the intent of hearing preservation, or a tumor previously irradiated with single-fraction GKRS. The immobilization device used for all patients was the Extend system (Leksell Gamma Knife Perfexion, Elekta, Kungstengsgatan, Stockholm). RESULTS: We identified 34 patients treated with fractionated GKRS between August 2013 and February 2015. There were a total of 37 tumors treated including 15 meningiomas, 11 pituitary adenomas, 6 brain metastases, 4 vestibular schwannomas, and 1 hemangioma. At last follow-up, all 21 patients treated for perioptic tumors had stable or improved vision and all 4 patients treated for vestibular schwannoma maintained serviceable hearing. No severe adverse events were reported. CONCLUSION: Fractionated GKRS was well tolerated in the treatment of large meningiomas, perioptic tumors, vestibular schwannomas with intent of hearing preservation, and reirradiation of previously treated tumors. ABBREVIATIONS: CNS, central nervous system; GKRS, Gamma Knife radiosurgery; SRS, stereotactic radiosurgery.

Minerva Endocrinologica.2016;41(3):366-76.Epub 2016/02/24

Gamma knife radiosurgery for pituitary adenomas

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Pituitary adenomas are frequently occurring intracranial neoplasms. The aim of the treatment of pituitary adenomas is to normalize hormonal hypersecretion, to preserve the normal pituitary function, to reserve or treat impaired pituitary function and to control tumor growth and its mechanical effects on the surrounding structures. Treatment modalities include surgical, medical and radiation therapy. Radiosurgery is mainly used as a secondary line treatment after surgery for residual or recurrent tumors. The antiproliferative effect is achieved by LKG irradiation in more than 90% of patients. Regarding the functioning pituitary adenomas, the manifestation of the treatment effect is slow and depends mainly on the type of adenoma. Gamma knife irradiation is safe when the maximal doses to pituitary and infundibulum are respected.

Surg Neurol Int.2015;6(Suppl 7):S279-83. Epub 2015/06/13

Percutaneous transluminal angioplasty in a patient with internal carotid artery stenosis following gamma knife radiosurgery for recurrent pituitary adenoma

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BACKGROUND: Intracranial vascular complications following radiosurgery are extremely rare. CASE DESCRIPTION: We report a case of stenosis in the internal carotid artery 5 years after gamma knife radiosurgery for a recurrent pituitary adenoma. Percutaneous transluminal angioplasty was performed successfully with anatomical and functional improvement. CONCLUSION: These results suggested the importance of monitoring for arterial stenosis in the long-term follow-up. Moreover, this is the first case of endovascular treatment as an effective therapy for intracranial arterial stenosis due to radiotherapy.

Int J Radiat Oncol Biol Phys.2015;91(5):1114. Epub 2015/04/04

In reply to Chen and Chung

Xu, Z., Schlesinger, D. and Sheehan, J. P., Departments of Neurological Surgery and Radiation Oncology, University of Virginia, Charlottesville, Virginia.

Int J Radiat Oncol Biol Phys.2015;91(5):1113-4. Epub 2015/04/04

Progression rate of silent corticotroph adenomas after stereotactic radiosurgery. In regard to Xu et al

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World Neurosurg.2015;Epub 2015/02/24

Stereotactic Radiosurgery as the Initial Treatment for Patients with Nonfunctioning Pituitary Adenomas

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OBJECTIVE: The aim of this study was to confirm the efficacy and safety of stereotactic radiosurgery as the initial treatment for patients with nonfunctioning pituitary adenomas (NFPAs), and to decide the optimum dose to achieve long-term tumor control as well as preservation of pituitary endocrine function. METHODS: The study

was a single-center retrospective analysis of 16 patients with primary NFPAs treated using gamma knife surgery (GKS). Fifteen of 16 NFPAs were growing to the suprasellar region and slightly compressing or very close to the optic apparatus. Initial GKS was selected to avoid visual disturbance caused by further tumor growth that would require surgical resection under general anesthesia. The median tumor volume was 2.0 cm³, and the median tumor margin dose was 15 Gy. RESULTS: The median clinical follow-up period was 98 months. The last follow-up images demonstrated tumor regression in 15 patients, and stable tumor in 1. No patient developed tumor progression. One patient who had pituitary apoplexy before treatment required hormone replacements 2 years after GKS. The other patients did not experience pituitary insufficiency requiring hormone replacements during the clinical follow-up period. No patient developed cranial nerve injury or radiation-induced neoplasm. CONCLUSIONS: GKS was a safe and effective treatment option in patients with primary NFPAs, especially for patients with advanced age or comorbidity. Attention should be paid to late adverse radiation effects such as hypopituitarism, optic neuropathy, and radiation-induced neoplasms. However, stereotactic radiosurgery with a conformal treatment plan sparing the normal pituitary gland will contribute to avoidance of such complications as well as achievement of long-term tumor control.

Acta Neurochir (Wien). 2014 Oct;156(10):1947-51. doi: 10.1007/s00701-014-2187-5. Epub 2014 Jul 26.

Intraoperative fat placement in surgically refractory parasellar neoplasms to facilitate stereotactic radiosurgery.

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BACKGROUND:

In this article, we report on the technique of placing fat in between a sellar or parasellar neoplasm and the optic chiasm to possibly protect the optic chiasm from sequelae of radiation.

METHODS:

A review was performed on three patients, each of whom had planned subtotal resection with fat placed near their optic chiasm to facilitate future radiosurgery.

RESULTS:

Follow-up on our three patients varied from 6 months to 3 years post-stereotactic radiosurgery. The fat remained stable and in place. The tumors either remained stable or reduced in size. No infections, postoperative marker dependent neurological complications or unusual symptoms were encountered.

CONCLUSIONS:

Placement of fat between a parasellar neoplasm and the optic chiasm appears to be a safe approach to help define the tumor chiasm space, helping to facilitate radiosurgery. Future experience is warranted to determine the efficacy of this technique.

Front Oncol. 2014 Apr 9;4:73. eCollection 2014.

Effect of treatment modality on the hypothalamic-pituitary function of patients treated with radiation therapy for pituitary adenomas: hypothalamic dose and endocrine outcomes.

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BACKGROUND:

Both fractionated external beam radiotherapy and single fraction radiosurgery for pituitary adenomas are associated with the risk of hypothalamic-pituitary (HP) axis dysfunction.

OBJECTIVE:

To analyze the effect of treatment modality (Linac, TomoTherapy, or gamma knife) on hypothalamic dose and correlate these with HP-axis deficits after radiotherapy.

METHODS:

Radiation plans of patients treated post-operatively for pituitary adenomas using Linac-based 3D-conformal radiotherapy (CRT) (n = 11), TomoTherapy-based intensity modulated radiation therapy (IMRT) (n = 10), or gamma knife stereotactic radiosurgery (n = 12) were retrospectively reviewed. Dose to the hypothalamus was analyzed and post-radiotherapy hormone function including growth hormone, thyroid stimulating hormone, adrenocorticotropic hormone, prolactin, and gonadotropins (follicle stimulating hormone/luteinizing hormone) were assessed.

RESULTS:

Post-radiation, 13 of 27 (48%) patients eligible for analysis developed at least one new hormone deficit, of which 8 of 11 (72%) occurred in the Linac group, 4 of 8 (50%) occurred in the TomoTherapy group, and 1 of 8 (12.5%) occurred in the gamma knife group. Compared with fractionated techniques, gamma knife showed improved hypothalamic sparing for DMax Hypo and V12Gy. For fractionated modalities, TomoTherapy showed improved dosimetric characteristics over Linac-based treatment with hypothalamic DMean (44.8 vs. 26.8 Gy $p = 0.02$), DMax (49.8 vs. 39.1 Gy $p = 0.04$), and V12Gy (100 vs. 76% $p = 0.004$).

CONCLUSION:

Maximal dosimetric avoidance of the hypothalamus was achieved using gamma knife-based radiosurgery followed by TomoTherapy-based IMRT, and Linac-based 3D conformal radiation therapy, respectively.

Neurosurgery.2014;Epub 2014/06/06

Dose-Volume Analysis of Radiation-Induced Optic Neuropathy After Single-Fraction Stereotactic Radiosurgery

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Background

The risk of radiation-induced optic neuropathy (RION) is the primary limitation of single-fraction stereotactic radiosurgery (SRS) for many patients with para-sellar lesions.

Objective

To define the normal tissue complication probability (NTCP) of the anterior visual pathways (AVP) after single-fraction SRS. Methods: Retrospective review comparing visual function before and after SRS in 133 patients (266 sides) with pituitary adenomas having SRS between October 2007 and July 2012. Patients with prior radiation therapy or SRS were excluded. The median follow-up after SRS was 32 months.

Results

The median maximum point dose to the AVP was 9.2 Gy (IQR, 6.9-10.8). One hundred seventy-four sides (65%) received >8 Gy: the median 8-Gy volume was 15.8 mm (IQR, 3.7-36.2). Ninety-four sides (35%) received >10 Gy; the median 10-Gy volume was 1.6 mm (IQR, 0.5-5.3). Twenty-nine sides (11%) received >12 Gy; the median 12-Gy volume was 0.1 mm (IQR, 0.1-0.6). No patient had a RION after SRS. The chances of developing a RION at the 8-Gy, 10-Gy, and 12-Gy volumes (95% CI) in this series were 0-2.6%, 0-4.7%, and 0-13.9%, respectively.

Conclusion

The AVP in patients without prior radiation treatments can safely receive radiation doses up to 12 Gy with a low risk of RION. Although additional studies are needed to better delineate the NTCP of the AVP, adherence to the AVP radiation tolerance guidelines developed 20 years ago (8 Gy) limits the applicability and potentially the effectiveness of single-fraction SRS for patients with lesions in the para-sellar region.

J Korean Med Sci. 2014 Mar;29(3):405-10. Epub 2014 Feb 27.

Clinicopathologic analysis of pituitary adenoma: a single institute experience.

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Pituitary adenoma (PA) is a common benign neuroendocrine tumor; however, the incidence and proportion of hormone-producing PAs in Korean patients remain unknown. Authors analyzed 506 surgically resected and pathologically proven pituitary lesions of the Seoul National University Hospital from 2006 to 2011. The lesions were categorized as: PAs ($n = 422$, 83.4%), Rathke's cleft cysts (RCCs) ($n = 54$, 10.6%), inflammatory lesions ($n = 8$, 1.6%), meningiomas ($n = 4$), craniopharyngiomas ($n = 4$), granular cell tumors ($n = 1$), metastatic renal cell carcinomas ($n = 2$), germinomas ($n = 1$), ependymomas ($n = 1$), and unsatisfactory specimens ($n = 9$, 1.8%). PAs were slightly more prevalent in women (M: F = 1:1.17) with a mean age of 48.8 yr (9-80 yr). Immunohistochemical analysis revealed that prolactin-producing PAs (16.6%) and growth hormone-producing adenomas (9.2%) were the most common functional PAs. Plurihormonal PAs and nonfunctioning (null cell) adenomas were found in 14.9% and 42.4% of patients with PAs, respectively. The recurrence rate of PAs was 11.1%, but nearly 0% for the remaining benign lesions such as RCCs. 25.4% of patients with PAs were treated by gamma-knife after surgery

due to residual tumors or regrowth of residual tumor. In conclusion, the pituitary lesions and the proportions of hormone-producing PAs in Korean patients are similar to those of previous reports except nonfunctioning (null cell) PAs, which are unusually frequent.

Acta Neurochir Suppl. 2013;116:49-54.

Role of gamma knife radiosurgery in the management of pituitary adenomas and craniopharyngiomas.

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INTRODUCTION:

Radical microsurgical removal of pituitary adenomas (PAs) and craniopharyngiomas (CPHs) is often difficult. In such cases radiosurgery can be used as a second-line treatment option.

MATERIALS AND METHODS:

Our series included 436 PAs and 164 CPHs. The majority of patients had large or giant tumors and were treated with microsurgery. Additionally, between June 2008 and August 2011, a total of 29 PAs and 10 CPHs underwent radiosurgery using Leksell Gamma Knife Perfexion. At the time of treatment the volume of the PAs varied from 0.6 to 26.0 cm³ (mean 5.9 cm³) and that of the CPHs from 0.19 to 17.0 cm³ (mean 6.6 cm³). The marginal doses ranged from 12 to 15 Gy (mean 14.5 Gy) for nonsecreting PAs, from 22 to 25 Gy (mean 24 Gy) for hormone-secreting PAs, and from 8 to 14 Gy (mean 11 Gy) for CPHs.

RESULTS:

The postoperative mortality rates after surgical removal of PAs via the transsphenoidal approach and craniotomy were 2.4 % and 8.0 %, respectively, whereas after surgery for CPH it was 5.9 %. No major complications were noted in our limited number of patients after radiosurgical treatment. Taking into consideration only cases with radiological follow-up of at least 12 months, shrinkage of the tumor was demonstrated in 5 of 11 patients with a PA and in 4 out of 6 patients with a CPH.

CONCLUSION:

Radiosurgery is safe and effective second-line management option in cases of recurrent or residual PA or CPH. Occasionally, it can be applied even as a primary treatment in selected patients.

Acta Neurol Belg. 2013 Dec;113(4):463-7. doi: 10.1007/s13760-013-0211-9. Epub 2013 May 25.

Long-term tumor control of benign intracranial tumors after Gamma Knife radiosurgery in 280 patients followed more than 5 years.

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The objective of the study was to assess the long-term radiological outcome of benign intracranial tumors (BIT) after Gamma Knife radiosurgery. We report the radiological outcome of 280 patients who underwent radiosurgical irradiation for BIT in a single center. Our series included 120 meningiomas, 139 vestibular schwannomas, 12 other schwannomas and 9 pituitary adenomas. Serial imaging studies were performed after irradiation for at least 5 years for all patients. The median tumor volume was 1.9 cc, and the median margin dose was 12 Gy. After a median follow-up of 6.8 years, the tumor control rate was 92.1%: tumor decreased in 176 cases (62.9%), remained unchanged in 82 lesions (29.3%) and increased in 22 cases (7.9%). The actuarial tumor control rate was 93.2% at 5 years, 92.3% at 7.5 years and 91.0% at 10 years. No atypical or malignant transformation of irradiated tumors occurred during the follow-up period. Gamma Knife radiosurgery provides a high rate of tumor control for BIT even in the medium to long-term.

Neurosurg Clin N Am. 2013 Oct;24(4):509-19. doi: 10.1016/j.nec.2013.05.005. Epub 2013 Jul 1.

Stereotactic radiosurgery of pituitary adenomas.

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The goal of pituitary adenoma radiosurgery is to halt tumor growth, normalize hormonal hypersecretion if present, maintain normal pituitary function, and preserve important structures around the sella. The radiation dose necessary to stop tumor growth is lower than the dose necessary to achieve normalization of hormonal hypersecretion. The minimum distance required between the irradiated target and the optic pathway should be 2 mm for secreting adenomas, but in cases of nonsecreting adenomas this distance is even lower. The current

role of radiosurgery in most cases is as an adjuvant treatment of residual or recurrent adenomas after previous microsurgery.

Can J Neurol Sci. 2013 Jul;40(4):546-52.

Gamma knife in the treatment of pituitary adenomas: results of a single center.

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INTRODUCTION:

Gamma Knife (GK) radiosurgery for pituitary adenomas can offer a means of tumor and biologic control with acceptable risk and low complication rates.

METHODS:

Retrospective review of all the patients treated at our center with GK for pituitary adenomas from Nov 2003 to June 2011.

RESULTS:

We treated a total of 86 patients. Ten were lost to follow-up. Mean follow was 32.8 months. There were 21 (24.4%) growth hormone secreting adenomas (GH), 8 (9.3%) prolactinomas (PRL), 8 (9.3%) adrenocorticotrophic hormone secreting (ACTH) adenomas, 2 (2.3%) follicle stimulating hormone/luteinizing hormone secreting (FSH/LH) adenomas, and 47 (54.7%) null cell pituitary adenomas that were treated. Average maximum tumor diameter and volume was 2.21cm and 5.41cm³, respectively. The average dose to the 50% isodose line was 14.2 Gy and 23.6 Gy for secreting and non-secreting adenomas respectively. Mean maximal optic nerve dose was 8.87 Gy. Local control rate was 75 of 76 (98.7%), for those with followup. Thirty-three (43.4%) patients experienced arrest of tumor growth, while 42 (55.2%) patients experienced tumor regression. Of the 39 patients with secreting pituitary tumors, 6 were lost to follow-up. Improved endocrine status occurred in 16 (50.0%), while 14 (43.8%) demonstrated stability of hormone status on continued pre-operative medical management. Permanent complications included: panhypopituitarism (4), hypothyroidism (4), hypocortisolemia (1), diabetes insipidus (1), apoplexy (1), visual field defect (2), and diplopia (1).

CONCLUSIONS:

Gamma Knife radiosurgery is a safe and effective means of achieving tumor growth control and endocrine remission/stability in pituitary adenomas.

Neurosurgery. 2013 Apr;72(4):630-7; 636-7.

Hypopituitarism after stereotactic radiosurgery for pituitary adenomas.

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BACKGROUND:

Studies of new-onset Gamma Knife stereotactic radiosurgery (SRS)-induced hypopituitarism in large cohort of pituitary adenoma patients with long-term follow-up are lacking.

OBJECTIVE:

We investigated the outcomes of SRS for pituitary adenoma patients with regard to newly developed hypopituitarism.

METHODS:

This was a retrospective review of patients treated with SRS at the University of Virginia between 1994 and 2006. A total of 262 patients with a pituitary adenoma treated with SRS were reviewed. Thorough endocrine assessment was performed immediately before SRS and in regular follow-ups. Assessment consisted of 24-hour urine free cortisol (patients with Cushing disease), serum adrenocorticotrophic hormone, cortisol, follicle-stimulating hormone, luteinizing hormone, insulin-like growth factor-1, growth hormone, testosterone (men), prolactin, thyroid-stimulating hormone, and free T(4).

RESULTS:

Endocrine remission occurred in 144 of 199 patients with a functioning adenoma. Tumor control rate was 89%. Eighty patients experienced at least 1 axis of new-onset SRS-induced hypopituitarism. The new hypopituitarism rate was 30% based on endocrine follow-up ranging from 6 to 150 months; the actuarial rate of new pituitary hormone deficiency was 31.5% at 5 years after SRS. On univariate and multivariate analyses, variables regarding the increased risk of hypopituitarism included suprasellar extension and higher radiation dose to the tumor margin; there were no correlations among tumor volume, prior transsphenoidal adenomectomy, prior radiation therapy, and age at SRS.

CONCLUSION:

SRS provides an effective and safe treatment option for patients with a pituitary adenoma. Higher margin radiation dose to the adenoma and suprasellar extension were 2 independent predictors of SRS-induced hypopituitarism.

Neurosurg Clin N Am. 2012 Oct;23(4):571-86. doi: 10.1016/j.nec.2012.06.011. Epub 2012 Aug 14.

External beam radiation therapy and stereotactic radiosurgery for pituitary adenomas.

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This article discusses contemporary use of external beam radiotherapy and stereotactic radiosurgery for pituitary adenoma patients. Specific techniques are discussed. In addition, indications and outcomes, including complications, are detailed.

World Neurosurg. 2012 Jul;78(1-2):58-9. Epub 2011 Nov 1.

Comparing radiation therapy and radiosurgery for pituitary adenoma patients.

Pollock BE1.

Comment on

Neurocognitive changes in pituitary adenoma patients after gamma knife radiosurgery: a preliminary study. [World Neurosurg. 2012]

Technol Cancer Res Treat. 2012 Apr;11(2):117-22.

Prospective study of the short-term adverse effects of gamma knife radiosurgery.

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Purpose of this study is to determine the types, incidence, and severity of acute complications of intracranial stereotactic radiosurgery (SRS), specifically Gamma Knife (GK). Patients who had never had previous SRS were eligible for this prospective IRB-approved study. The questionnaire used applicable questions from CTCAE v.3.0, the Brief Pain Questionnaire (Short Form), Brief Fatigue Inventory, and the Tinnitus Handicap Inventory. Questionnaires were obtained prior to Gamma Knife (GK), 1 week, 1 month, and 2 months to assess complications. Seventy-six eligible patients (median age of 62 years) had complete data and were analyzed. Diagnoses included: 26 (34%) with brain metastases, 15 (20%) with trigeminal neuralgia, 12 (16%) with schwannoma, 10 (13%) with meningioma, 7 (9%) with arteriovenous malformation, 3 (4%) with pituitary adenoma, and 3 (4%) with other. At 1 week, 24% developed minimal scalp numbness ($p = 0.0004$ baseline compared to 1 week). Only 13% had minimal scalp numbness at 1 month and 2% at 2 months (both $p = NS$ compared to baseline). There was no difference in scalp tingling between baseline and the various time points. Thirteen percent developed pin site pain at 1 week with a median intensity level of 2 out of 10. By one month, only 3% had pin site pain with a median intensity level of 3 out of 10. Four percent developed pin-site infection at 1 week and none at 1 and 2 months. There was no significant difference in nausea from baseline at 1 week, but there was worsening nausea at 1 month ($p = 0.0114$). By 1 month, 10% reported new local hair loss. 23%, 16%, and 15% complained of new/worsening fatigue at 1 week, 1 month, and 2 months, respectively, but 40% reported fatigue at baseline. Balance improved following SRS over all time periods (for all comparisons, $p < 0.009$). 1%, 6%, and 3% developed new tinnitus at 1 week, 1 month, and 2 months, respectively, which was significant when comparing baseline to non-baseline ($p = 0.0269$). Thirty-two patients were employed prior to SRS. Three (9%) patients did not return to work. Twenty-seven (84%) patients returned to work a median of 4 days after SRS. Two people did not report their employment status after SRS. There was no significant difference in face swelling, headache, eye pain, vomiting, seizures, or passing out at any intervals compared to baseline. This prospective study demonstrates that GK is well tolerated with few patients developing major acute effects. Many patients are able to return to work shortly after GK.

Curr Opin Endocrinol Diabetes Obes. 2011 Aug;18(4):278-88.

Recent advances in pituitary tumor management.

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PURPOSE OF REVIEW:

Advances in the neurosurgical management of pituitary tumors have included the refinement of surgical access and significant progress in navigation technology to help further reduce morbidity and improve outcome. Similarly, stereotactic radiosurgery has evolved to become an integral part in pituitary tumors not amenable to medical or surgical treatment.

RECENT FINDINGS:

The evolution of minimally invasive surgery has evolved toward endoscopic versus microscopic trans-sphenoidal approaches for pituitary tumors. Debate exists regarding each approach, with advocates for both championing their cause. Stereotactic and fractional radiosurgery have been shown to be a safe and effective means of controlling tumor growth and ensuring hormonal stabilization, with longer-term data available for GammaKnife compared with CyberKnife.

SUMMARY:

The advances in trans-sphenoidal surgical approaches, navigation technological improvements and the current results of stereotactic radiosurgery are discussed.

World Neurosurg. 2012 Jul;78(1-2):122-8. Epub 2011 Nov 7.

Neurocognitive changes in pituitary adenoma patients after gamma knife radiosurgery: a preliminary study.

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Author information

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Abstract

OBJECTIVE:

We evaluated the effects of gamma-knife radiosurgery (GKRS) on the cognitive functioning of patients with a pituitary adenoma.

METHODS:

A total of 14 patients with pituitary adenomas were enrolled in this neurocognitive study. Nine patients had Cushing disease, and five had nonfunctioning pituitary adenomas. Five patients underwent GKRS for their pituitary adenomas. Other treatment modalities included transsphenoidal resection and conservative management. Comparisons were made between treatment groups and between those with Cushing disease versus those with a nonfunctioning adenoma by the use of psychometric tests of general intellectual functioning, memory, and current mood state. These tests were the Symptom Checklist 90 Revised, Wechsler Test of Adult Reading, Wechsler Memory Scale-third edition, selected subtests of the Wechsler Adult Intelligence Scale-third edition, and the Delis-Kaplan Executive Function System.

RESULTS:

When analyzed collectively, the patient group showed deficits in immediate memory ($t=-2.70$, $P=0.02$) and high levels of psychological distress (46% of patients) in the presence of intact general intellectual functioning. No neurocognitive differences were found between the GKRS treated group versus participants not treated with GKRS ($t\leq 0.70$, $P\geq 0.39$). Similarly, no appreciable neurocognitive differences were demonstrated between those with nonfunctioning adenomas as compared with those with Cushing disease ($t\leq 1.56$, $P\geq 0.15$).

CONCLUSIONS:

We found no evidence that GKRS impairs the neurocognitive functioning of patients with pituitary disease above any impairment caused by the disease itself. Further studies will require approximately 20 patients in each comparison group to confirm this result.

J Neurosurg. 2011 Feb;114(2):354-8. Epub 2010 May 14.

Temozolomide-induced inhibition of pituitary adenoma cells.

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OBJECT:

Aggressive pituitary adenomas frequently require multimodality treatment including pituitary-suppressive medications, microsurgery, and radiation therapy or radiosurgery. The effectiveness of temozolomide in terms of growth suppression and decreased hormonal production is evaluated.

METHODS:

Three pituitary adenoma cell lines--MMQ, GH3, and AtT20--were used. A dose escalation of temozolomide was performed for each cell line, and inhibition of cell proliferation was assessed using an MTT assay. Concentrations of temozolomide that produced statistically significant inhibition of cell proliferation for each cell type were

identified. Extent of apoptosis for each selected temozolomide concentration was studied using TUNEL staining. The effect of temozolomide on prolactin secretion in MMQ and GH3 cells was also measured via ELISA.

RESULTS:

Significant inhibition of cell proliferation was noted for MMQ and GH3 cells at a concentration of 250 μ M temozolomide. The AtT20 cells demonstrated statistically significant cell inhibition at a concentration of only 50 μ M temozolomide ($p < 0.05$). Apoptosis significantly increased in all cell lines in as little as 24 hours of incubation at the respective temozolomide concentrations ($p < 0.05$). Prolactin secretion in the prolactin secreting MMQ and GH3 cell lines was inhibited by 250 μ M temozolomide.

CONCLUSIONS:

Temozolomide inhibits cell proliferation and induces apoptotic cell death in aggressive pituitary adenoma cells. A reduction in hormonal secretion in prolactinoma cells was also afforded by temozolomide. Temozolomide may prove useful in the multimodality management of aggressive pituitary adenomas.

Endocr Pathol. 2011 Mar;22(1):10-7.

A case of corticotroph carcinoma that caused multiple cranial nerve palsies, destructive petrosal bone invasion, and liver metastasis.

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A 52-year-old woman experienced sudden onset of double vision due to a right abducens nerve palsy and was diagnosed as having a pituitary macroadenoma that invaded into the right cavernous sinus. Otherwise, she was asymptomatic despite marked elevation of ACTH (293 pg/ml) and cortisol (24.6 μ g/dl) levels. The patient underwent transsphenoidal surgery followed by γ -knife radiosurgery (GKR), which healed the diplopia and ameliorated the hypercortisolemia. The excised tumor was diffusely stained for ACTH with a high (15%) Ki-67 labeling index. Early tumor recurrence occurred twice thereafter, producing right lower cranial nerve palsies with petrosal bone destruction at 8 months and an ipsilateral oculomotor nerve palsy at 12 months after GKR; all palsies resolved completely with the second and third GKRs. Hypercortisolemia worsened rapidly soon after the third GKR, and the patient developed marked weight gain, hypokalemia, and hypertension. Multiple liver lesions were incidentally detected with computer tomography and identified as metastatic pituitary tumor on immunohistochemistry. An ACTH-producing adenoma should be followed carefully for early recurrence and/or metastatic spread when the tumor is an invasive macroadenoma with a high proliferation marker level. The unique aggressive behavior and high potential for malignant transformation of this case are discussed.

Eur J Endocrinol. 2011 Feb;164(2):169-78. Epub 2010 Nov 11.

Is it possible to avoid hypopituitarism after irradiation of pituitary adenomas by the Leksell gamma knife?

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OBJECTIVE:

Radiation therapy is one of the treatment options for pituitary adenomas. The most common side effect associated with Leksell gamma knife (LGK) irradiation is the development of hypopituitarism. The aim of this study was to verify that hypopituitarism does not develop if the maximum mean dose to pituitary is kept under 15Gy and to evaluate the influence of maximum distal infundibulum dose on the development of hypopituitarism.

DESIGN AND METHODS:

We followed the incidence of hypopituitarism in 85 patients irradiated with LGK in 1993-2003. The patients were divided in two subgroups: the first subgroup followed prospectively (45 patients), irradiated with a mean dose to pituitary <15Gy; the second subgroup followed retrospectively 1993-2001 and prospectively 2001-2009 (40 patients), irradiated with a mean dose to pituitary >15Gy. Serum TSH, free thyroxine, testosterone or 17 β -oestradiol, IGF1, prolactin and cortisol levels were evaluated before and every 6 months after LGK irradiation.

RESULTS:

Hypopituitarism after LGK irradiation developed only in 1 out of 45 (2.2%) patients irradiated with a mean dose to pituitary <15Gy, in contrast to 72.5% patients irradiated with a mean dose to pituitary >15Gy. The radiation dose to the distal infundibulum was found as an independent factor of hypopituitarism with calculated maximum safe dose of 17 Gy.

CONCLUSION:

Keeping the mean radiation dose to pituitary under 15 Gy and the dose to the distal infundibulum under 17 Gy prevents the development of hypopituitarism following LGK irradiation.

Neurosurg Rev. 2010 Apr;34(2):181-9. Epub 2010 Sep 14.

Treatment of pituitary adenomas using radiosurgery and radiotherapy: a single center experience and review of literature.

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Fractionated radiotherapy (FRT) and gamma knife stereotactic radiosurgery (GKSRS) are used as adjuvant therapies to surgical resection for functional and non-functional pituitary adenomas, although their optimum role in the treatment algorithm, as well as long-term safety and efficacy, still awaits further study. We report a single center experience with 33 patients with non-functional (16 patients), ACTH- (five patients), GH- (four patients), or prolactin-secreting (eight patients) tumors treated with FRT or SRS. The median tumor diameter was 1.9 cm, and the median follow-up was 36 months. For GKSRS, the median dosage was 16 Gy for non-functional adenomas and 23 Gy for hormone-secreting tumors. The median total dose for FRT was 50.4 Gy over 28 fractions (median). Two patients (6%) demonstrated radiographic evidence of tumor progression, three patients (9%) demonstrated radiation-induced visual field deficits on neuro-ophthalmic evaluation, and two patients (6%) suffered from radiation-induced hypopituitarism. Biochemical control, defined as normalized hormone values in the absence of medical therapy, was achieved in five out of eight prolactinoma patients and two out of five patients with Cushing's disease, but none of the four patients with acromegaly. These results are presented with a review of the relevant literature on the differential characteristics of FRT versus SRS in the treatment of functional and non-functional pituitary adenomas and validate postoperative irradiation as a potentially safe and effective means for tumor control.

J Neurosurg. 2010 Dec;113 Suppl:144-8.

Leksell GammaPlan version 10.0 preview: performance of the new inverse treatment planning algorithm applied to Gamma Knife surgery for pituitary adenoma.

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OBJECT:

Treatment planning for Gamma Knife surgery has traditionally been a forward planning (FP)-only approach with results that depend significantly on the experience of the user. Leksell GammaPlan version 10.0, currently in beta testing, introduces a new inverse planning (IP) engine that may allow more reproducible results across dosimetrists and individual institutions. In this study the authors compared the FP and IP approaches to Gamma Knife surgery.

METHODS:

Forty-three patients with pituitary adenomas were evaluated after dose planning was performed using FP and IP treatment approaches. Treatment plans were compared for target coverage, target selectivity, Paddick gradient index, number of isocenters, optic pathways dose, and treatment time. Differences between the forward and inverse treatment plans were evaluated in a statistical fashion.

RESULTS:

The IP software generated a dose plan within approximately 10 minutes. The FP approach delivered the prescribed isodose to a larger treatment volume than the IP system ($p < 0.001$). The mean (\pm SD) FP and IP coverage indices were 0.85 ± 0.23 and 0.85 ± 0.13 , respectively (no significant difference). The mean FP and IP gradient indices were 2.78 ± 0.20 and 3.08 ± 0.37 , respectively ($p < 0.001$). The number of isocenters did not appreciably differ between approaches. The maximum doses directed to the optic apparatus for the FP and IP methods were 8.67 ± 1.97 Gy and 12.33 ± 5.86 Gy, respectively ($p < 0.001$).

CONCLUSIONS:

The Leksell GammaPlan IP system was easy to operate and provided a reasonable, first approximation dose plan. Particularly in cases in which there are eloquent structures at risk, experience and user-based optimization will be required to achieve an acceptable Gamma Knife dose plan.

J Neurosurg. 2010 Jan;112(1):118-21. doi: 10.3171/2009.6.JNS081176.

Gamma knife surgery for lymphocytic hypophysitis.

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Lymphocytic hypophysitis is a relatively uncommon autoimmune inflammatory disorder affecting the pituitary gland. It most frequently occurs in women of child-bearing age. The authors report on their experience with a patient who presented with diplopia and marked enlargement of the pituitary gland. She underwent transsphenoidal surgery, and histopathological analysis confirmed the diagnosis of lymphocytic hypophysitis. The disease proved refractory to resection, and any attempt at withdrawal of corticosteroid therapy resulted in a return of the patient's symptoms and enlargement of the sellar contents. The patient underwent Gamma Knife surgery (GKS) to the sella and both cavernous sinuses. After GKS, the patient was able to discontinue steroid therapy without return of her symptoms. Follow-up MR images demonstrated no evidence of recurrence of lymphocytic hypophysitis. For persistent lymphocytic hypophysitis, GKS is a reasonable treatment option.

Neurosurgery. 2010 Jul;67(1):27-32; discussion 32-3.

Factors associated with endocrine deficits after stereotactic radiosurgery of pituitary adenomas.

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OBJECTIVE:

To analyze the factors associated with anterior pituitary deficits after pituitary adenoma stereotactic radiosurgery (SRS).

METHODS:

The tumor, pituitary stalk, and pituitary gland were segmented on the dose plans of 82 patients (secreting tumors, n = 53; nonsecreting tumors, n=29) for dose-volume analysis. No patient had undergone prior radiation therapy and all patients had at least 12 months of endocrinological follow-up (median, 63 months; mean, 69 months; range, 13-134).

RESULTS:

Thirty-four patients (41%) developed new anterior pituitary deficits at a median of 32 months (range, 2-118) after SRS. The risk of developing new anterior pituitary deficits was 16% and 45% at 2 and 5 years, respectively. Multivariate analysis of the entire group showed that poor visualization of the pituitary gland (hazard ratio [HR]=2.63, 95% confidence interval [CI]=1.10-6.25, P=.03) was associated with a higher rate of new anterior pituitary deficits. Dosimetric analysis of 60 patients whose pituitary gland could be clearly identified showed that increasing mean pituitary gland radiation dose correlated with new anterior pituitary deficits (HR=1.11, 95% CI=1.02-1.20, P=.02). New anterior pituitary deficits stratified by mean pituitary gland radiation dose: ≤ 7.5 Gy, 0% (0/7); 7.6 to 13.2 Gy, 29% (7/24); 13.3 to 19.1 Gy, 39% (9/23); >19.1 Gy, 83% (5/6).

CONCLUSION:

New endocrine deficits after pituitary adenoma radiosurgery were correlated with increasing radiation dose to the pituitary gland. Methods that limit the radiation dose to the pituitary gland during SRS may increase the probability of preserving pituitary function.

Neurol Med Chir (Tokyo). 2010;50(9):737-48.

Role of γ knife radiosurgery in neurosurgery: past and future perspectives.

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The gamma knife was the first radiosurgical device developed at the Karolinska Institute in 1967. Stereotactic radiosurgery using the gamma knife has been widely accepted in clinical practice and has contributed to the development of neurosurgery. More than 500,000 patients have been treated by gamma knife stereotactic radiosurgery so far, and the method is now an indispensable neurosurgical tool. Here we review long-term outcomes and development of stereotactic radiosurgery using the gamma knife and discuss its future perspectives. The primary role of stereotactic radiosurgery is to control small well-demarcated lesions such as metastatic brain tumors, meningiomas, schwannomas, and pituitary adenomas while preserving the function of surrounding brain tissue. The gamma knife has been used as a primary treatment or in combination with surgery, and some applications have been accepted as standard treatment in the field of neurosurgery. Treatment of cerebral arteriovenous malformations has also been drastically changed after emergence of this technology. Controlling functional disorders is another role of stereotactic radiosurgery. There is a risk of radiation-induced adverse events, which are usually mild and less frequent. However, especially in large or invasive lesions, those risks are not negligible and pose limitations. Advancement of irradiation technology and dose planning software have enabled more sophisticated and safer treatment, and further progress will contribute to better treatment outcomes not only for brain lesions but also for cervical lesions with less invasive treatment.

Neurol Med Chir (Tokyo). 2010;50(9):749-55.

Stereotactic radiosurgery/radiotherapy for pituitary adenomas: a review of recent literature.

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The recent clinical results are reviewed of stereotactic radiosurgery/radiotherapy for the treatment of pituitary adenomas. The outcomes of pituitary adenomas treated by stereotactic radiosurgery/radiotherapy with gamma knife, CyberKnife, or linear accelerator (LINAC) radiosurgery were evaluated from articles published after 2004. Each study was evaluated for the number of patients, radiosurgical parameter (marginal dose), length of follow up, tumor growth control, rate of hormonal normalization in secretory adenomas, and adverse events. After gamma knife radiosurgery, the tumor reduction rates varied from 42.3% to 89% in non-secreting adenomas. However, the tumor control rates in non-secreting adenomas were more than 90% in most studies. In growth hormone-secreting adenomas, the rates of insulin-like growth factor-1 normalization ranged from 36.9% to 82%. In adrenocorticotropin-secreting adenomas, the rates for 24-hour urine free cortisol normalization ranged from 27.9% to 54%. In prolactin-secreting adenomas, the prolactin normalization ranged from 17.4% to 50%. New hormonal deficits ranged from 0% to 34%. New visual deficits were relatively low. The number of patients treated with CyberKnife and LINAC radiosurgery/radiotherapy was small and follow-up periods were relatively short compared to those with gamma knife treatment, but the clinical outcomes after these therapies were similar to those after gamma knife therapy. Image-guided stereotactic radiosurgery/radiotherapy with the gamma knife, CyberKnife, or LINAC system is effective and safe against pituitary adenomas. Careful long-term follow up of the patients is necessary because of long-term anti-tumor effects and delayed adverse events.

J Neurooncol. 2010 Jun;98(2):185-94. doi: 10.1007/s11060-010-0172-2. Epub 2010 Apr 22.

Gamma Knife robotic microradiosurgery of pituitary adenomas invading the cavernous sinus: treatment concept and results in 89 cases.

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The objective of the present retrospective study was evaluation of results of "robotic microradiosurgery" of pituitary adenomas invading the cavernous sinus. Eighty-nine patients with such tumors underwent management using Leksell Gamma Knife model C with automatic positioning system. There were 77 residual and 12 recurrent neoplasms. The applied radiosurgical treatment plan was based on the use of multiple isocenters, mainly of smaller size, which were positioned compactly within the border of the lesion with resultant improved dose homogeneity, increased average dose within the target, and sharp dose fall outside the treated volume. The marginal dose varied from 12 to 25 Gy (mean, 18.2 Gy) in non-functional pituitary adenomas (43 cases), and from 12 to 35 Gy (mean, 25.2 Gy) in hormone-secreting ones (46 cases). The length of follow-up after treatment ranged from 24 to 76 months (mean, 36 months). Control of the tumor growth was attained in 86 cases (97%), whereas actual shrinkage of the lesion was marked in 57 cases (64%). In 18 out of 46 secreting neoplasms (39%), normalization of the excess of the pituitary hormone production was noted after radiosurgery. Treatment-associated morbidity was limited to transitory cranial nerve palsy in two patients (2%). No patient with either non-functional or hormone secreting tumor exhibited new pituitary hormone deficit after treatment. In conclusion, highly precise microanatomy-based Gamma Knife robotic microradiosurgery provides an opportunity for effective management of pituitary adenomas invading the cavernous sinus with preservation of the adjacent functionally important neuronal structures.

J Neurosurg. 2010 Dec;113 Suppl:153-59.

Pituitary insufficiency as a side effect after radiosurgery for pituitary adenomas: the role of the hypothalamus.

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OBJECT:

Causes of pituitary insufficiencies as a side effect of Gamma Knife surgery (GKS) following irradiation of the hypothalamopituitary axis are still under debate. In an investigation of pituitary insufficiencies after GKS, the authors' main focus is on what role can be attributed to the hypothalamus with regard to endocrinological changes in hypothalamopituitary function following GKS.

METHODS:

A total of 108 patients consecutively treated between April 1992 and July 2003 were included in this retrospective study. All patients had undergone either transsphenoidal or transcranial surgery prior to GKS. The spot dosimetry method was used to determine doses delivered to structures of the hypothalamopituitary axis. For statistical analyses, endocrine insufficiency and deterioration in pituitary function were defined as a decrease in hormonal blood levels below the normal range for 1 or more anterior pituitary lobe hormones. Additionally, an analysis of the rate of patients requiring hormone replacement therapy after GKS due to new endocrinopathies was performed.

RESULTS:

Complete patient records of 61 male and 47 female patients with a mean age of 51.9 years (range 9.1–81.2 years) were available for our investigation. The overall tumor control rate was 97% and the endocrinological cure rate was 61.2%. Mean treatment doses in patients with and without new endocrine insufficiencies (shown as with/without insufficiencies and followed by probability values) were as follows: 1.3/0.8 Gy to the hypothalamus ($p = 0.2$); 2.2/1.6 Gy to the median eminence ($p = 0.1$); 6.5/4.1 Gy to the pituitary stalk ($p = 0.004$); and 12.4/9.5 Gy to the pituitary gland ($p = 0.05$). The median overall duration of follow-up after GKS was 6.7 years, with 84 patients (77.7%) whose follow-up was longer than 12 months. The median follow-up time after GKS in patients who developed a new pituitary dysfunction was 79.5 months (6.6 years, SD 3.8 years), and the median follow-up time in patients with no new insufficiencies was 78.4 months (6.5 years, SD 4 years).

CONCLUSIONS:

Gamma Knife surgery is a safe and effective treatment for patients with residual and recurrent pituitary adenomas. The rate of pituitary insufficiencies after GKS is still lower than that after conventional radiotherapy. Very low radiation doses are directed to the hypothalamus, and thus this structure does not play a major role in the development of pituitary insufficiencies after GKS. The results of this study show that patients in whom the pituitary stalk and pituitary gland receive a high mean point dose are more likely to develop pituitary insufficiencies after GKS than those who receive a lower dose.

Radiat Oncol. 2010 Nov 17;5:109.

Radiosurgery for pituitary adenomas: evaluation of its efficacy and safety.

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OBJECT:

To assess the effects of radiosurgery (RS) on the radiological and hormonal control and its toxicity in the treatment of pituitary adenomas.

METHODS:

Retrospective analysis of 42 patients out of the first 48 consecutive patients with pituitary adenomas treated with RS between 1999 and 2008 with a 6 months minimum follow-up. RS was delivered with Gamma Knife as a primary or adjuvant treatment. There were 14 patients with non-secretory adenomas and, among functioning adenomas, 9 were prolactinomas, 9 were adrenocorticotrophic hormone-secreting and 10 were growth hormone-secreting tumors. Hormonal control was defined as hormonal response (decline of more than 50% from the pre-RS levels) and hormonal normalization. Radiological control was defined as stasis or shrinkage of the tumor. Hypopituitarism and visual deficit were the morbidity outcomes. Hypopituitarism was defined as the initiation of any hormone replacement therapy and visual deficit as loss of visual acuity or visual field after RS.

RESULTS:

The median follow-up was 42 months (6-109 months). The median dose was 12.5 Gy (9 - 15 Gy) and 20 Gy (12 - 28 Gy) for non-secretory and secretory adenomas, respectively. Tumor growth was controlled in 98% (41 in 42) of the cases and tumor shrinkage occurred in 10% (4 in 42) of the cases. The 3-year actuarial rate of hormonal control and normalization were 62.4% and 37.6%, respectively, and the 5-year actuarial rate were 81.2% and 55.4%, respectively. The median latency period for hormonal control and normalization was, respectively, 15 and 18 months. On univariate analysis, there were no relationships between median dose or tumoral volume and hormonal control or normalization. There were no patients with visual deficit and 1 patient had hypopituitarism after RS.

CONCLUSIONS:

RS is an effective and safe therapeutic option in the management of selected patients with pituitary adenomas. The short latency of the radiation response, the highly acceptable radiological and hormonal control and absence of complications at this early follow-up are consistent with literature.

Nat Rev Endocrinol. 2010 Apr;6(4):214-23. Epub 2010 Feb 23.

Role of stereotactic radiosurgery in the management of pituitary adenomas.

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Trans-sphenoidal neurosurgery is the gold standard treatment for pituitary adenomas, but it can be contraindicated or ineffective. Stereotactic radiosurgery is a procedure aimed at controlling hormone hypersecretion and tumor size of pituitary adenomas. This Review discusses the long-term efficacy and adverse effects of stereotactic radiosurgery with the Gamma Knife((R)) in secreting and nonsecreting pituitary adenomas. Long-term data confirm the antisecretory efficacy of the procedure (about 50% remission in hypersecreting tumors) but also a previously unknown low risk of recurrence (2-10% of cases). The time to remission is estimated to range from 12 to 60 months. The antitumoral efficacy of this treatment against nonsecreting tumors is observed in about 90% of cases. Hypopituitarism is the main adverse effect, observed in 20-40% of cases. Comparisons with conventional fractionated radiotherapy reveal a lower rate of remission with Gamma Knife((R)) radiosurgery, counterbalanced by a more rapid efficacy and a lower rate of hypopituitarism. Short-term follow-up results on stereotactic fractionated radiotherapy suggest a risk of hypopituitarism similar to the one observed with radiosurgery. Therefore, stereotactic radiosurgery is probably still useful to treat some cases of pituitary adenoma, despite the fact that antisecretory drugs, particularly for acromegaly and prolactinomas, are becoming more effective and are well tolerated, thus increasing the probability of success with nonsurgical therapy.

Discov Med. 2010 Aug;10(51):107-11.

Gamma Knife radiosurgery in pituitary adenomas: Why, who, and how to treat?

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

Eur J Endocrinol. 2009 Dec;161(6):819-28. Epub 2009 Sep 22.

Gamma knife radiosurgery: a safe and effective salvage treatment for pituitary tumours not controlled despite conventional radiotherapy.

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OBJECTIVE:

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

PATIENTS AND METHODS:

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

RESULTS:

Following GK, mean GH fell by 49% at 1 year in patients with somatotroph tumours. Serum IGF1 fell by 32% at 1 year and by 38% at 2 years. To date, 80% of the patients with acromegaly have achieved normalisation of IGF1, and 30% have also achieved a mean GH level of <1.8 ng/ml correlating with normalised mortality. A total of 75% NFPAs showed disease stabilisation or shrinkage post GK. The patient with a prolactinoma showed a dramatic response: 75% reduction in prolactin at 2 years, with a marked shrinkage on magnetic resonance imaging. The results in corticotroph adenomas were variable. Prior to GK, 72% of the patients were panhypopituitary, and 42%

of the remainder have developed new anterior pituitary hormone deficiencies to date. No other adverse events have been detected at a mean follow-up of 36.4 months.

CONCLUSIONS:

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

J Neurooncol. 2009 May;92(3):337-43. Epub 2009 Apr 9.

Stereotactic radiosurgery of benign intracranial tumors.

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Stereotactic radiosurgery is a frequently performed procedure for patients with benign intracranial tumors. Benign tumors are good candidates for radiosurgery because they are generally non-invasive, are well visualized by magnetic resonance imaging, and their slow rate of proliferation makes conventional radiation dose fractionation unnecessary. Stereotactic radiosurgery is now an important part of both neurosurgical and radiation oncology training. This chapter will review the indications and results of radiosurgery for patients with intracranial meningiomas, vestibular schwannomas, and pituitary adenomas having single-fraction radiosurgery at the Mayo Clinic since 1990.

Prog Neurol Surg. 2009;22:77-95. doi: 10.1159/000163384.

Long-term results of stereotactic gamma knife radiosurgery for pituitary adenomas. Specific strategies for different types of adenoma.

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Long-term results of gamma knife radiosurgery for pituitary adenomas are presented and treatment strategies for different adenoma types are discussed. Two hundred and sixty-seven patients with pituitary adenoma have been treated by gamma knife radiosurgery during the past 12 years. There were 131 cases of nonfunctioning and 136 cases of functioning adenomas, in which 71 GH-producing, 33 PRL-producing and 32 ACTH-producing adenomas were included. Retreatment with the gamma knife was done in 8 cases because of large tumors or uncontrolled hormones. Micro- and small adenomas could be cured by gamma knife radiosurgery alone. Surgical or chemical debulking was necessary before radiosurgery for a large tumor with extrasellar extension. Retreatment was effective and safe in some cases. Nonfunctioning adenomas showed higher control rates than functioning adenomas even with lower dose treatment. Cushing disease showed the best response because of the smallest tumor size with the highest dose treatment. Acromegaly and prolactinoma were difficult to control because of larger tumors with lower dose treatment. The rate of hormone normalization was also high in Cushing disease but lower in prolactinoma and lowest in acromegaly. High-dose treatment was necessary for functioning adenomas to control tumor growth and oversecretion of hormones. In conclusion, gamma knife radiosurgery was effective and safe for the treatment of pituitary adenomas. However, the treatment strategies should be specific to each adenoma type according to the radiosensitivity, chemosensitivity and biological nature of the tumor.

Surg Neurol. 2009 Sep;72(3):248-55; discussion 255-6. doi: 10.1016/j.surneu.2008.06.003. Epub 2008 Sep 11.

Stereotactic radiosurgery for pituitary metastases.

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BACKGROUND:

We evaluated the role of Gamma Knife SRS in the multidisciplinary management of metastatic cancer to the pituitary gland.

METHODS:

We retrospectively reviewed records of 18 consecutive pituitary metastasis patients who underwent Gamma Knife SRS during a 21-year experience. The median patient age was 57.6 years (range, 27.0-81.1 years). There were 5 patients who had initial surgical resection of their pituitary metastasis, 5 who had fractionated radiation, and 7 who had CT before SRS. The median radiosurgery target volume was 3.5 mL (range, 0.2-18.0 mL), and the median marginal dose was 13.0 Gy (range, 9-18 Gy).

RESULTS:

The overall survival after SRS at 3, 6, and 12 months, respectively, was 66%, 36%, and 18%. The median survival after SRS was 5.2 months. The progression-free survival after SRS was 100% and 66.7% at 6 and 12 months,

respectively. The only factor associated with an improved overall survival was younger age at presentation. Diabetes insipidus improved in 3 (42.9%) of 7 patients. Neurological symptoms or signs improved in 4 (50.0%) of 8 patients. Three (16.7%) patients developed new neurological deficits due to tumor progression despite SRS.

CONCLUSION:

Development of a pituitary metastasis is an ominous finding in the context of systemic cancer. Stereotactic radiosurgery is an effective palliative approach for most patients with pituitary metastasis.

J Neurooncol. 2009 May;92(3):345-56. doi: 10.1007/s11060-009-9832-5. Epub 2009 Apr 9.

Stereotactic radiosurgery for pituitary adenomas: a comprehensive review of indications, techniques and long-term results using the Gamma Knife.

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OBJECT:

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

METHODS:

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

RESULTS:

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

CONCLUSIONS:

Although the effectiveness of radiosurgery varies considerably depending on the adenoma histopathology, volume, and radiation dose, most studies indicate that radiosurgery when combined with microsurgery is effective in controlling pituitary adenoma growth and hormone hypersecretion. Long-term follow-up is essential to determine the rate of endocrinopathy, visual dysfunction, hormonal recurrence, and adenoma volume control.

J Neurosurg. 2008 Dec;109 Suppl:34-40. doi: 10.3171/JNS/2008/109/12/S7.

Use of hybrid shots in planning Perfexion Gamma Knife treatments for lesions close to critical structures.

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OBJECT:

The authors investigated the use of different collimator values in different sectors (hybrid shots) when treating patients with lesions close to critical structures with the Perfexion model Gamma Knife.

METHODS:

Twelve patients with various tumors (6 with a pituitary tumor, 3 with vestibular schwannoma, 2 with meningioma, and 1 with metastatic lesion) that were within 4 mm of the brainstem, optic nerve, pituitary stalk, or cochlea were considered. All patients were treated at the authors' institution between June 2007 and March 2008. The patients' treatments were replanned in 2 different ways. In the first plan, hybrid shots were used such that the steepest dose gradient was aligned with the junction between the target and the critical structure(s). This was accomplished by placing low-value collimators in appropriate sectors. In the second plan, no hybrid shots were used. Sector blocking (either manual or dynamic) was required for all plans to reduce the critical structure doses to acceptable levels. Prescribed doses ranged from 12 to 30 Gy at the periphery of the target. The plans in each pair were designed to be equally conformal in terms of both target coverage (as measured by the Paddick conformity index) and critical structure sparing.

RESULTS:

The average number of shots required was roughly the same using either planning technique (16.7 vs 16.6 shots with and without hybrids). However, for all patients, the number of blocked sectors required to protect critical

areas was larger when hybrid shots were not used. On average, nearly twice as many blocked sectors (14.8 vs 7.0) were required for the plans that did not use hybrid shots. The number of high-value collimators used in each plan was also evaluated. For small targets ($\leq 1 \text{ cm}^3$), for which 8 mm was considered a high value for the collimator, plans employing hybrids used an average of 2.3 times as many 8-mm sectors as did their nonhybrid counterparts (7.4 vs 3.2 sectors). For large targets ($> 1 \text{ cm}^3$), for which 16 mm was considered a high value for the collimator, hybrid plans used an average of 1.4 times as many 16-mm sectors as did the plans without hybrids (10.7 vs 7.7 sectors). Decreasing the number of blocked sectors and increasing the number of high-value collimator sectors led to use of shorter beam-on times. Beam-on times were 1-39% higher (average 17%) when hybrid shots were not allowed. The average beam-on time for plans with and without hybrid shots was 67.4 versus 78.4 minutes.

CONCLUSIONS:

The judicious use of hybrid shots in patients for whom the target is close to a critical structure is an efficient way to achieve conformal treatments while minimizing the beam-on time. The reduction in beam-on time with hybrid shots is attributed to a reduced use of blocked sectors and an increased number of high-value collimator sectors.

Neurosurg Focus. 2008;24(5):E11. doi: 10.3171/FOC/2008/24/5/E11.

The principles of skull base radiosurgery.

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Stereotactic radiosurgery is commonly used for selected patients with benign cranial base tumors. The goal of radiosurgery is cessation of tumor growth and preservation of neurological function. Over the last 2 decades, the technique of radiosurgery has evolved due to improved imaging, better radiosurgical devices and software, and the continued analysis of results. In this report, the authors discuss technical concepts and dose selection in skull base radiosurgery.

Ai Zheng. 2007 Jul;26(7):742-7.

[Efficacy of total removal or subtotal removal combined gamma knife radiation on giant pituitary adenoma: a report of 160 cases].

[Article in Chinese]

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BACKGROUND & OBJECTIVE:

Pituitary adenoma, a kind of familiar benign intracranial tumor, is mainly treated with surgical operation, medication, and radiation. However, the outcome, especially for giant pituitary adenoma, is not very satisfactory. This study was to explore the efficacy of total tumor removal or subtotal tumor removal combined gamma knife radiation on giant pituitary adenoma.

METHODS:

Clinical data of 160 giant pituitary adenoma patients were analyzed. Of the 160 patients, 90 received total tumor removal, 70 received subtotal tumor removal combined gamma knife radiation. The symptom improvement, tumor size change, serum hormone concentration, complications after treatment, and so on, of the 2 groups were compared.

RESULTS:

At 12 months after treatment, the efficiency rate, recurrence rate, and mortality were 74.4%, 31.1%, and 3.3%, respectively, in total tumor removal group; however, the efficiency rate reached 91.4%, the recurrence rate decreased to 11.4%, and no patients died in combined therapy group. The follow-up results at 24 months after treatment and at present (over 5 years) showed that though the efficiency rate had descended and recurrence rate or mortality had ascended in both groups, the efficacy of combined therapy was obviously better than that of total tumor removal. The decrease of serum hormone concentration was more obvious in combined therapy group than in total tumor removal group at 12 months after treatment. Moreover, total tumor removal group had more serious complications than combined therapy group after treatment.

CONCLUSION:

Subtotal tumor removal combined gamma knife radiation is better than total tumor removal for giant pituitary adenoma.

Prog Neurol Surg. 2007;20:172-9.

Pathological findings following radiosurgery of pituitary adenomas.

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Pituitary adenomas represent approximately 10-20% of all primary brain tumors. Surgical resection is the mainstay of treatment for most pituitary adenomas. At times, complete surgical resection may be impossible or the adenoma may recur. The Gamma Knife has become an important neurosurgical tool for the treatment of recurrent or residual pituitary adenomas. Gamma surgery typically affords a high rate of tumor volume control but a more variable rate of endocrinological remission. When radiosurgery fails to provide a good outcome, surgical resection often needs to be repeated. At the University of Virginia during a 15-year time period, 434 patients have been treated for recurrent or residual pituitary adenomas with the Gamma Knife. Upon review of their follow-up neuroimaging studies, we have not observed a case of a radiation-induced neoplasm. The incidence of Gamma Knife-induced neoplasia is likely low and will require longer follow-up to ascertain the true incidence. Preand post-Gamma Knife histological specimens were available in 4 patients (0.92% of patients). A comparison of these specimens was significant for necrosis but not vessel wall hyaline thickening, fibrinoid necrosis, vascular occlusions, or teleangiectatic dilatations. Further study must be performed to determine the histological changes that accompany the frequently beneficial effects of radiosurgery in recurrent or residual pituitary adenomas.

Prog Neurol Surg. 2007;20:164-71.

Radiosurgery for pituitary adenomas.

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Stereotactic radiosurgery has been used to manage patients with pituitary adenomas for over 30 years. Numerous studies have documented that more than 95% of pituitary adenoma patients have either tumor shrinkage or stabilization after radiosurgery. Biochemical remission is possible in approximately 80% of properly selected patients with hormone-producing pituitary adenomas. The time to endocrine normalization typically ranges from 1 to 5 years. Factors associated with endocrine cure include the absence of pituitary suppressive medications at the time of radiosurgery and higher radiation doses. Delayed anterior pituitary deficits occur in 20-50% of patients depending on the length and quality of the endocrine follow-up. Visual loss after radiosurgery is rare if the maximum radiation dose to the optic apparatus is kept below 12 Gy. Since the effects of radiosurgery are gradual compared to surgical removal of pituitary adenomas, surgical resection remains the primary therapy for the majority of patients with large tumors causing visual loss or for patients with symptomatic acromegaly or Cushing's disease. However, radiosurgery is effective for pituitary adenoma patients with persistent or recurrent tumors after prior surgery, or for patients considered high risk for open surgical procedures due to coexisting medical conditions.

Neurol Med Chir (Tokyo). 2007 Oct;47(10):483-5.

Delayed cerebrospinal fluid leakage 10 years after transsphenoidal surgery and gamma knife surgery - case report.

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A 38-year-old woman presented with repeated episodes of meningitis. She had undergone transsphenoidal tumor removal followed by gamma knife irradiation in 1994. Complete remission was achieved. Intermittent cerebrospinal fluid (CSF) leakage began in 2004, and transsphenoidal surgery was performed for direct repair of the skull base defect. Operative findings showed that the sellar floor was uncovered, and CSF continuously escaped through the cyanoacrylate polymer framework of the previous repair. Reconstruction used autologous muscle pieces and cyanoacrylate polymer adhesive. The CSF leakage was presumably due to delayed radiation damage to the mucous membrane of the skull base. Several methods for reconstruction of the sellar floor have been proposed, which all rely on tissue regeneration including the arachnoid, dura mater, and mucous membrane of the sphenoidal sinus. Preservation of the arachnoid membrane and minimizing removal of the mucous membrane are essential, especially if postoperative irradiation is anticipated.

Cancer. 2007 Aug 15;110(4):854-60.

The efficacy of fractionated radiotherapy and stereotactic radiosurgery for pituitary adenomas: long-term results of 125 consecutive patients treated in a single institution.

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BACKGROUND:

The objective of this retrospective cohort study was to define the efficacy and safety of fractionated radiotherapy (FRT) and stereotactic radiosurgery (SRS) for the treatment of patients with pituitary adenoma.

METHODS:

Between January 1995 and April 2006, 125 consecutive patients with pituitary adenomas (54 hormone-secreting adenomas and 71 nonsecretory adenomas) received FRT or underwent SRS. Sixty-four patients received FRT, for which the mean total dose was 50.4 grays (Gy) (range, 48-54 Gy), and 61 patients underwent gamma-knife SRS with mean marginal dose of 25.1 Gy (range, 9-30 Gy).

RESULTS:

After mean follow up of 36.7 months, the tumor volume was increased in only 4 patients (3.2%). The overall actuarial progression-free survival rate was 99% at 2 years and 97% at 4 years. No difference was observed between the FRT group and the SRS group in the control of tumor growth. Based on the endocrinologic results in the patients who had secretory adenomas, the overall hormone complete remission rate was 26.2% at 2 years and 76.3% at 4 years. The median time to complete remission was 26 months in the SRS group and 63 months in the FRT group ($P = .0068$). Hypopituitarism developed as a delayed complication in 11.5% of patients at a median of 84 months.

CONCLUSIONS:

Both FRT and SRS were efficient treatment modalities for the control of tumor growth in patients with pituitary adenomas. The current results indicated that single-dose radiosurgery more promptly produces an effect on the hypersecretion of pituitary hormones and may be recommended over FRT for suitable patients.

Int J Radiat Oncol Biol Phys. 2007 Nov 1;69(3):852-7. Epub 2007 Jun 14.

Outcome after pituitary radiosurgery for thalamic pain syndrome.

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PURPOSE:

To evaluate outcomes after pituitary radiosurgery in patients with post-stroke thalamic pain syndrome.

METHODS AND MATERIALS:

From 2002 to 2006, 24 patients with thalamic pain syndrome underwent pituitary radiosurgery at Tokyo Women's Medical University and were followed at least 12 months thereafter. The radiosurgical target was defined as the pituitary gland and its connection with the pituitary stalk. The maximum dose varied from 140 to 180 Gy. Mean follow-up after treatment was 35 months (range, 12-48 months).

RESULTS:

Initial pain reduction, usually within 48 h after radiosurgery, was marked in 17 patients (71%). However, in the majority of cases the pain recurred within 6 months after treatment, and at the time of the last follow-up examination durable pain control was marked in only 5 patients (21%). Ten patients (42%) had treatment-associated side effects. Anterior pituitary abnormalities were marked in 8 cases and required hormonal replacement therapy in 3; transient diabetes insipidus was observed in 2 cases, transient hyponatremia in 1, and clinical deterioration due to increase of the numbness severity despite significant reduction of pain was seen once.

CONCLUSIONS:

Pituitary radiosurgery for thalamic pain results in a high rate of initial efficacy and is accompanied by acceptable morbidity. It can be used as a primary minimally invasive management option for patients with post-stroke thalamic pain resistant to medical therapy. However, in the majority of cases pain recurrence occurs within 1 year after treatment.

Front Horm Res. 2006;34:185-205.

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

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Pituitary adenomas are not just one of the most common intracranial tumors but also one of the most difficult to cure. Neurosurgeons have adapted their tools to include precise ionizing radiation in the form of the gamma

knife to treat pituitary adenomas. The use of the gamma knife in the management of pituitary adenomas following microsurgery or in selected cases as a primary treatment is safe. The combined application of transsphenoidal surgery and Gamma Knife surgery is beneficial in many difficult cases. However in some patients, optimal control of tumor growth and normalization of hypersecretory states are not achieved. Innovative improvements in operative and radiosurgical techniques are required to avoid pituitary insufficiency and to reduce the number of the cases in which optimal radiosurgery is not feasible because of close tumor proximity to the optic pathways.

J Neurosurg. 2006 Dec;105 Suppl:241-8.

Shielding strategies for Gamma Knife surgery of pituitary adenomas.

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OBJECT:

The relative performances of two plugging strategies commonly used for pituitary adenoma dose plans were evaluated in terms of factors that influence dose plan quality.

METHODS:

Dose plans and clinical treatment data were obtained in 108 patients treated with the Model C Gamma Knife at the University of Virginia. These data were analyzed to determine factors (including plugging strategy) influencing the quality of the dose plans in terms of beam time, conformity, dose to the optic apparatus, and plugging burden. For both secretory and nonsecretory adenomas, beam time ($p(\text{secretory}) < 0.001$, $p(\text{nonsecretory}) = 0.015$) and plugging burden ($p(\text{secretory}) = 0.007$, $p(\text{nonsecretory}) = 0.038$) were reduced when using the customized plugging strategy. The choice of plugging strategy was found to play no significant role in conformity or dose to the optic apparatus. Other factors found to play a significant role in adenoma dose plan quality included tumor volume, prescription dose, and distance from the target to the optic pathways.

CONCLUSIONS:

While both plugging strategies were effective at providing the required protection to the optic pathways, the authors found that the customized plugging strategy provided more efficient performance in pituitary adenoma treatments.

J Neurosurg. 2006 Dec;105 Suppl:37-42.

Stereotactic radiosurgery for metastatic tumors in the pituitary gland and the cavernous sinus.

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OBJECT:

Metastases to the pituitary gland and cavernous sinus occasionally occur. Metastases of this nature are problematic because they are adjacent to eloquent structures such as cranial nerves, including the optic pathways and nerves for extraocular movement and facial sensation. Stereotactic radiosurgery has been reported to be safe and effective for metastases in various sites of brain parenchyma, providing the tumors are not large. Radiosurgery can be performed to treat a precisely defined target, and the risk of radiation side effects on the surrounding structures is reduced. The results of Gamma Knife surgery (GKS) for the treatment of metastases in the pituitary gland and the cavernous sinus are evaluated.

METHODS:

Among 623 patients with brain metastases treated by GKS, 13 patients (2.1%) had pituitary and/or cavernous metastases. The primary malignancies included lung cancer (five cases), breast cancer (two cases), parotid cancer (two cases), renal cell carcinoma, thyroid cancer, nasal cancer, and gastrointestinal stromal tumor (one case each). The location of the tumors was the pituitary gland (Type 1) in four patients, the cavernous sinus (Type 2) in five patients, and both the cavernous sinus and the sellar region (Type 3) in four patients. The patients' symptoms included dysfunction of the pituitary gland (two patients), visual disturbance (four patients), oculomotor palsy (one patient), abducent palsy (five patients), and trigeminal dysfunction (five patients). A margin dose of 12 to 12.3 Gy was delivered to pituitary metastases. A margin dose of 14.4 to 20 Gy was delivered to cavernous lesions. The dose selection depended on the spatial relationship between tumors and the cranial nerves. Imaging and clinical follow-up data have been obtained in nine of 13 patients for 2 to 12 months (median 4 months) after GKS. Three pituitary and/or cavernous tumors are stable in size, and six tumors have disappeared or decreased in size; full or partial improvement of visual function, extraocular movement, and facial sensation have been achieved in these six patients.

CONCLUSIONS:

These preliminary results seem to indicate that GKS is a safe and effective treatment for pituitary and cavernous metastases, as it is effective for parenchymal metastases and promptly improved some patients' symptoms.

J Neurosurg. 2006 Dec;105 Suppl:26-30.

Gamma Knife surgery for invasive pituitary macroadenoma.

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OBJECT:

Pituitary adenomas have been treated using a variety of modalities including resection, medication, fractionated radiotherapy, and stereotactic radiosurgery. The policy has been that all adenomas should first be treated with resection to reduce the volume of the tumor. The authors' study was conducted to determine the efficacy of using Gamma Knife surgery (GKS) for pituitary adenomas invading the cavernous sinus.

METHODS:

Of 397 patients with pituitary tumors who underwent GKS between October 1994 and October 2005, 68 patients had pituitary macroadenomas invading the cavernous sinus. Sixty-seven cases were available for follow up. The mean age of the patients in these cases was 42.8 years (range 14-73 years). The male/female ratio was 0.8:1. The mean adenoma volume was 9.3 cm³. A total of 24 patients had undergone craniotomies and resection, and 11 patients had undergone transsphenoidal surgery prior to GKS. The mean follow-up period was 32.8 months. Tumor control was defined as a decrease or no change in tumor volume after GKS. Endocrinological improvement was defined as a decline in hormone levels to below 50% of the pre-GKS level. Tumor control was achieved in 95.5% of the cases. Endocrinological improvement was achieved in 68% of 25 patients. One patient suffered hypopituitarism after GKS.

CONCLUSIONS:

Gamma Knife surgery is a safe and effective treatment for invasive pituitary macroadenoma with few complications.

J Neurosurg. 2006 Dec;105 Suppl:12-7.

Image-guided microradiosurgery for skull base tumors: advantages of using gadolinium-enhanced constructive interference in steady-state imaging.

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Gamma Knife surgery (GKS) is image-guided surgery for brain tumors. Precise tumor visualization is needed in dose planning to control tumor progression. The surrounding vital structures must also be clearly defined to allow the preservation of their function. A special magnetic resonance (MR) imaging sequence was chosen for use with GKS to treat skull base and suprasellar tumors. Gadolinium-enhanced 0.5-mm constructive interference in steady-state (CISS) slices were obtained in skull base and suprasellar tumors. Each structure that was adjacent to the tumor could be visualized more clearly by using this imaging technique because the tumor became transparent even though there was no change in the appearance of the surrounding structures after injection of Gd. Use of this technique in acoustic tumors allowed the seventh and eighth cranial nerves to be visualized in the cisternal and intrameatal portions; both of which were distinguishable from the tumor. Suprasellar tumor could be distinguished from the adjacent optic pathway. The use of Gd-enhanced CISS imaging allowed for optimal dose planning with very high conformity in every tumor. Achieving this high conformity allowed the preservation of adjacent structures and their functions. Establishing optimal dose planning in brain tumors is very important to overcome the problem of producing new neurological deficits in patients who may already be suffering disease-related deficits. The use of this special CISS MR imaging sequence may help accomplish this goal.

J Neurosurg. 2005 Apr;102(4):678-91.

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

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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.

Nat Clin Pract Endocrinol Metab. 2005 Nov;1(1):2-3.

Pituitary adenomas: is Gamma Knife radiosurgery safe?

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Rev Neurol (Paris). 2005 May;161(5):575-7.

[Intermittent diplopia after prolonged downward gaze to the right: what is the differential diagnosis?].

[Article in French]

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In general, intermittent diplopia evokes suspicion of ocular myasthenia gravis. However, other etiologies such as Brown syndrome or myokymia of the superior oblique may provoke intermittent diplopia. We present a case of intermittent diplopia due to a tumor in the cavernous sinus. A 59-year-old patient reported intermittent diplopia after prolonged downward gaze to the right. All other gaze directions failed to provoke symptoms. In 1992, the diagnosis of inactive macroadenoma of the pituitary gland was established and the patient underwent surgery and radiation therapy. At physical examination, prolonged downward gaze to the right of about 2 minutes provoked paresis of abduction, slight ptosis, and restriction of elevation on the left side, corresponding to sixth nerve palsy and palsy of the superior branch of the third nerve on the left side. MRI showed a relapse of the macroadenoma with infiltration of the cavernous sinus on the left side. The patient underwent surgery then focal radiation (gamma-knife). The clinical course was favourable and at the follow-up examination six months later, no diplopia was reported.

J Neurosurg. 2005 Jan;102 Suppl:38-41.

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

Hayashi M1, Taira T, Ochiai T, Chernov M, Takasu Y, Izawa M, Kouyama N, Tomida M, Tokumaru O, Katayama Y, Kawakami Y, Hori T, Takakura K.

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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.

Endocrine. 2005 Oct;28(1):87-92.

Gamma knife radiosurgery for pituitary adenomas.

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Although surgical extirpation by transsphenoidal microsurgery is a major remedy for pituitary adenomas, adjuvant therapy also plays an important role in achieving tumor growth control and endocrine normalization in hormone-secreting tumors. Historically, the treatment options for pituitary adenomas included microsurgery, medical management, and fractionated radiotherapy, but radiosurgery has recently emerged as a practical treatment option. In this paper, we will describe the indications, radiosurgical procedure, results, histological change, and complications of gamma knife radiosurgery (GKS) for pituitary adenomas based on our experience since 1991 and a review of the literature.

Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2004 Aug;29(4):463-6.

[Gamma knife treatment for pituitary adenomas].

[Article in Chinese]

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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.

Rivista Medica.2004;10(1-2):25-30. Epub

The role of gamma knife radiosurgery in the management of pituitary adenomas

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Surgery is the first choice for the treatment of pituitary adenomas. Gamma knife radiosurgery is a safe and effective adjuvant therapy for recurrent or residual adenomas. Good results in tumor growth control and endocrinological improvement or cure are frequently achieved. Complication rate is very low.

Prakticky Lekar.2004;84(3):133-139. Epub

Application of radiosurgery in the treatment of pituitary adenoma

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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.

J Nucl Med. 2004 Jul;45(7):1146-54.

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

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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.

J Neurooncol. 2004 Aug-Sep;69(1-3):257-72.

Stereotactic radiosurgery for pituitary adenomas: a review of the literature.

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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.

Pituitary. 2003;6(1):53-8.

Effect of gamma knife radiosurgery on a pituitary gonadotroph adenoma: a histologic, immunohistochemical and electron microscopic study.

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The morphologic findings in a pituitary macroadenoma removed from a 65-year old man by the transsphenoidal approach 9 months after gamma knife surgery are reported. The tumor was immunoreactive for FSH beta and showed ultrastructural features consistent with an oncocytic gonadotroph adenoma. Accumulation of connective tissue separating small groups of adenoma cells was evident. Several dilated vessels and numerous vascular endothelial growth factor immunopositive adenoma cell were noted. By electron microscopy the endothelial linings frequently showed discontinuities with platelet accumulation attached to the gaps. Several vessels were severely injured showing necrosis of endothelial cells. It can be concluded that gamma knife surgery caused severe alterations in pituitary adenoma microcirculation indicating that vascular injury plays a crucial role in tumor shrinkage.

Neurosurgery. 2003 Feb;52(2):309-16; discussion 316-7.

Radiation tolerance of functioning pituitary tissue in gamma knife surgery for pituitary adenomas.

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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.

Japanese Journal of Neurosurgery.2003;12(5):337-342. Epub

Gamma knife radiosurgery for pituitary adenomas: Indications and treatment outcomes

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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 nonfunctioning 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.

Neurosurgery. 2003 Jul;53(1):51-9; discussion 59-61.

Gamma knife radiosurgery for pituitary adenoma: early results.

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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(3), 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.

Chinese Journal of Clinical Rehabilitation.2003;7(2):349. Epub

Pituitary apoplexy after gamma knife treatment

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Biomed Pharmacother. 2002;56 Suppl 1:178s-181s.

Gamma knife radiosurgery for pituitary adenoma.

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For the treatment of pituitary adenomas, transsphenoidal surgery is established as a first choice of treatment. However, pituitary adenomas are often not curable with surgery alone, and further treatment including radiation therapy is required to control the disease. In this report, we review the literature of gamma knife radiosurgery for pituitary adenomas and discuss the efficacy of this modern technology. Radiosurgery achieved 85-100% of growth control rates with only mild and transient neurological complications in most cases. Endocrinological normalization was obtained in more than 65% of GH producing tumors. These hormonal control rates seemed to be slightly better in GH producing tumors compared to ACTH producing tumors. To normalize the excessive GH or ACTH levels, radiosurgery for functioning adenomas requires a relatively higher dose, ideally more than 35 Gy at tumor margin. However, the adjacent optic apparatus is less tolerable for irradiation, and the tumors have to be sufficiently separated from it to prevent the radiation-induced visual deficits. Therefore, the role of surgery should not be undervalued, and even if radiosurgery alone may be able to achieve an excellent outcome in some cases, surgical resection will remain the primary treatment for pituitary adenomas. For high-risk patients or patients with residual tumors after transsphenoidal surgery, gamma knife radiosurgery can be a first choice of treatment, achieving both growth control and hormonal remission with minimum neurological complications, which is equivalent to conventional radiation therapy but with much less risk of radiation injury to the surrounding structures.

Neuropathology. 2002 Mar;22(1):19-25.

Histological changes in the pituitary gland and adenomas following radiotherapy.

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To elucidate histological changes in the pituitary gland and adenomas following radiotherapy, two irradiated pituitary glands and seven irradiated non-functioning adenomas were studied. The latter included four cases with conventional radiation (CR) and three cases with radiosurgery: two with gamma knife radiosurgery (GKR) and one with stereotactic fractionated radiotherapy (SRT). The specimens were obtained 10 months to 10 years (mean 58 months) after the radiotherapy. Irradiated pituitary glands showed diffuse fibrosis in the adenohypophysis, whereas irradiated adenomas showed either mild or no fibrosis in five CR/SRT cases and diffuse thick hyaline deposits in two GKR cases. No necrosis was observed. Stellate-shaped S-100 protein-positive cells were greater in number in the irradiated pituitary glands than in the normal glands. Pituitary cells with dense granular reactivity for mitochondrial protein, cytochrome oxidase, and Mn-SOD, mimicking oncocytes, were greater in number in the irradiated adenohypophysis but did not show any change in cell size. Many irradiated pituitary cells and some irradiated adenoma cells were densely positive with anticytokeratin 1,5,10,14 antibody whereas non-irradiated counterparts were negative. In adenomas, MIB-1 labeling index remained unchanged after the radiation. The results may indicate that radiation-induced fibrosis was associated with an increased number of folliculo-stellate cells, mitochondrial dysfunction, and squamous metaplasia. These findings were prominent in irradiated pituitary cells and may participate in delayed pituitary hypofunction following

radiotherapy. In irradiated adenoma cells, similar findings were observed but diffuse fibrosis was absent. The histological changes were more intensive in adenomas following GKR than those following CR.

J Neurosurg. 2002 Dec;97(5 Suppl):542-50.

The integration of metabolic imaging in stereotactic procedures including radiosurgery: a review.

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OBJECT:

The authors review their experience with the clinical development and routine use of positron emission tomography (PET) during stereotactic procedures, including the use of PET-guided gamma knife radiosurgery (GKS).

METHODS:

Techniques have been developed for the routine use of stereotactic PET, and accumulated experience using PET-guided stereotactic procedures over the past 10 years includes more than 150 stereotactic biopsies, 43 neuronavigation procedures, and 34 cases treated with GKS. Positron emission tomography-guided GKS was performed in 24 patients with primary brain tumors (four pilocytic astrocytomas, five low-grade astrocytomas or oligodendrogliomas, seven anaplastic astrocytomas or ependymomas, five glioblastomas, and three neurocytomas), five patients with metastases (single or multiple lesions), and five patients with pituitary adenomas.

CONCLUSIONS:

Data obtained with PET scanning can be integrated with GKS treatment planning, enabling access to metabolic information with high spatial accuracy. Positron emission tomography data can be successfully combined with magnetic resonance imaging data to provide specific information for defining the target volume for the radiosurgical treatment in patients with recurrent brain tumors, such as glioma, metastasis, and pituitary adenoma. This approach is particularly useful for optimizing target selection for infiltrating or ill-defined brain lesions. The use of PET scanning contributed data in 31 cases (93%) and information that was specifically utilized to adapt the target volume in 25 cases (74%). It would seem that the integration of PET data into GKS treatment planning may represent an important step toward further developments in radiosurgery: this approach provides additional information that may open new perspectives for the optimization of the treatment of brain tumors.

J Neurosurg. 2002 Dec;97(5 Suppl):415-21.

Effects of gamma knife radiosurgery of pituitary adenomas on pituitary function.

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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 cm³ (range 0.2-14.6 cm³). 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.

Semin Ophthalmol. 2002 Mar;17(1):22-8.

Treatment of tumors involving the optic nerves and chiasm.

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An approach toward treatment of tumors involving the optic apparatus is presented. When tumors cause mass effect, microsurgical excision or debulking is generally recommended. Radiosurgery has been controversial yet advances in imaging and high speed computer planning allow treatment of lesions involving the optic apparatus with low morbidity. Microsurgical and radiosurgical approaches to tumors involving the globe, orbit, suprasellar region and third ventricle are discussed. Gamma Knife radiosurgery for choroidal melanomas spares orbital exenteration. We have used a marginal dose of 2025 Gy for choroidal melanomas and generally limit the optic nerves and chiasm to less than 10 Gy in other cases. The effective dose for cavernous hemangiomas remains unclear, however we have had success with marginal doses in the range of 1620Gy. Lower doses may prove successful yet better spare vision in cases where vision is useful. Our combined microsurgical and radiosurgical approach to tumors involving the apparatus has had an excellent rate of sparing vision, a low overall morbidity and excellent success.

J Neurosurg. 2002 Dec;97(5 Suppl):438-40.

Successful treatment of spindle cell sarcoma of the sella turcica. Case report.

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A primary spindle cell sarcoma of the sella turcica in a patient without a history of radiation treatment is a very rare occurrence. Only one other case has been reported to date, with local recurrence 7 months after the patient underwent subtotal resection and stereotactic radiosurgery of the tumor. The authors present a case of spindle cell sarcoma of the sella turcica successfully treated by surgery, external-beam radiotherapy, and gamma knife radiosurgery. After 24 months of follow up, the patient continues to show no evidence of disease.

Eur Neurol. 2002;47(1):61-3.

Early palliation of oculomotor nerve palsy following gamma knife radiosurgery for pituitary adenoma.

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AJR Am J Roentgenol. 2001 Oct;177(4):919-24.

MR imaging of pituitary adenomas after gamma knife stereotactic radiosurgery.

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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(3) (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.

J Neurooncol. 2001 Sep;54(2):197-203.

The role of gamma knife radiosurgery in the management of pituitary adenomas.

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No treatment modality has been entirely successful in the management of pituitary adenomas. Although most patients with pituitary microadenomas can be cured by transsphenoidal surgery, the results are less satisfactory in macroadenomas in particular with suprasellar and/or parasellar extension. Additional treatment is then called for. Conventional fractional radiotherapy can often control tumour growth but is limited to 45-50 Gy with a very slow reduction in elevated pituitary hormones and a high incidence of pituitary insufficiency. Stereotactic radiosurgery allows the delivery of radiation with high precision to the target with low doses to the surrounding tissues permitting higher radiation doses. Gamma knife radiosurgery using photon energy with gamma beams from multiple cobalt 60 radiation sources is now used in many centers. It can be carried out in an outpatient setting with one single treatment. A more rapid normalization of pituitary hormone hypersecretion than with conventional radiation can be achieved as well as arrest of tumour growth and reduction of tumour mass. We therefore consider gamma knife radiosurgery as a valuable compliment to pituitary surgery. Long-term prospective studies are needed to evaluate the frequency of pituitary insufficiency in patients where the target area is determined with stereotactic magnetic resonance imaging (MRI).

J Neurosurg. 2000 Dec;93 Suppl 3:2-5.

Stereotactic radiosurgery for pituitary adenoma invading the cavernous sinus.

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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.

J Neurosurg. 2000 Dec;93 Suppl 3:19-22.

Gamma knife radiosurgery for pituitary adenomas.

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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%.

Journal of Radiosurgery.1999;2(1):33-39. Epub

Adjuvant gamma-knife radiosurgery for a resected suprasellar pituitary adenoma with atypical immunohistochemistry: Case report

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A resected suprasellar mass was found to be an ectopic pituitary adenoma on light microscopy, but immunohistochemistry revealed unusual staining patterns. Residual disease was demonstrated on postoperative studies and γ -knife radiosurgery was used for treatment. The literature on ectopic pituitary tumors was reviewed. We concluded that postoperative stereotactic radiosurgery (SRS) for ectopic, suprasellar pituitary adenomas (and variants thereof) is an appropriate management option for persistent disease.

Stereotact Funct Neurosurg. 1999;72 Suppl 1:88-100.

A six year experience with the postoperative radiosurgical management of pituitary adenomas.

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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 ± 3 cm³ and the mean prescription dose was 13.8 ± 1.5 Gy. In the prolactinoma patients, the mean target volume was 6.7 ± 9 cm³ and the mean prescription dose was 14.2 ± 4 Gy. In the acromegalic patients, the mean target volume was 2.9 ± 2.5 cm³ and the mean prescription dose was 16 ± 4 Gy. ACTH secreting adenomas had a mean target volume of 3.6 ± 5.5 cm³ with a mean prescription dose of 17 ± 4.8 Gy. The mean follow-up time was 28.9 ± 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.

Stereotact Funct Neurosurg. 1999;72 Suppl 1:132-9.

Cerebral infarction with ICA occlusion after Gamma Knife radiosurgery for pituitary adenoma: A case report.

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Cranial irradiation may lead to accelerated atherosclerotic changes to small or medium sized arteries, but stroke associated with pituitary irradiation is not frequent. A patient treated with Gamma Knife radio-surgery (GKRS) for a pituitary adenoma suffered a cerebral infarction with internal carotid artery occlusion 4 years after radiosurgery. The patient was a 35-year-old male presenting with a visual disturbance. Endocrinological tests were normal. MRI revealed a 4.3 by 4.3 cm diameter invasive macroadenoma of the pituitary, projecting toward the suprasellar region and with cavernous sinus involvement with encasement of both internal carotid arteries (ICAs). GKRS was performed for residual tumor after a transcranial resection. The maximum dose was 40 Gy and the dose to the right carotid artery was below 20 Gy. The delayed hemiparesis was accompanied by a right capsular lacunar infarct shown on MRI. The images also showed a marked reduction in tumor size. Total, right ICA occlusion was confirmed by Doppler ultrasound. The patient had no history or signs of heart disease or metabolic disorder which could predispose to cerebrovascular.

Journal of Radiosurgery.1999;2(1):41. Epub

On 'Adjuvant gamma-knife radiosurgery for a resected suprasellar pituitary adenoma with atypical immunohistochemistry: Case report' (Videtic et al., this issue)

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Endocrinol Metab Clin North Am. 1999 Mar;28(1):133-42.

Role of gamma knife therapy in the management of pituitary tumors.

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1. Gamma knife therapy is an effective method of delivering radiation to pituitary tumors that have failed surgery and may be used as primary treatment in circumstances in which the patient refuses or is unsuitable for a transsphenoidal procedure. 2. Stereotactic radiosurgery with the gamma knife unit is generally administered in a single session unlike fractionated radiotherapy, which is administered four to five times per week over a 6-week period. 3. Preliminary data suggest that resolution of pituitary hypersecretion is faster with gamma knife therapy than with conventional radiotherapy. 4. Because of the nature of the gamma knife therapy and the fact that the radiation dose conforms to the tumor shape, there is a steep fall-off of radiation to surrounding tissue. Accordingly, the radiation dose to extrapituitary brain is substantially less with gamma knife radiosurgery than with conventional radiotherapy. This suggests that the development of second brain tumors and neurocognitive complications, which are significant risks with conventional radiotherapy, is much less likely with gamma knife surgery. 5. Gamma knife radiosurgery can be used to ablate tumors invading the cavernous sinus. 6. Gamma knife radiosurgery is safe as long as the dose of radiation to the optic structures is kept under 10 Gy. 7. Long-term follow-up is required for pituitary tumors treated by gamma knife therapy so as to determine its efficacy as well as its effects on pituitary function and any resultant complications.

Baillieres Best Pract Res Clin Endocrinol Metab. 1999 Oct;13(3):461-9.

Gamma knife radiosurgery for pituitary tumours.

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Stereotactic radiosurgery with the gamma knife delivers focused radiation from a cobalt-60 source in a single session to a pituitary tumour with minimal radiation to the adjacent normal brain tissue. Currently, gamma knife radiosurgery is predominantly used to treat failed pituitary surgery, although it has a role as a primary treatment for patients unwilling or unsuitable, for medical reasons, to undergo trans-sphenoidal surgery. The major risk from gamma knife radiosurgery is radiation damage to the visual pathways, but this can be avoided by limiting the radiation dose to the optic chiasm to under 10 Gy. In contrast, the neuronal and vascular structures running in the cavernous sinus are much less radiosensitive, allowing an ablative dose to be administered to tumours showing lateral invasion and impinging on cranial nerves III, IV, V and VI. Gamma knife radiosurgery appears to produce remission in secretory tumours faster than fractionated radiotherapy. Furthermore, the potential long-term risk of developing a second extra-pituitary brain tumour, as well as the neuropsychiatric effects associated with conventional radiation administration, seems less likely to occur with this form of treatment.

Stereotact Funct Neurosurg. 1999;72 Suppl 1:125-31.

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

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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.

Stereotact Funct Neurosurg. 1998 Oct;70 Suppl 1:119-26.

Pituitary adenomas: the effect of gamma knife radiosurgery on tumor growth and endocrinopathies.

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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.

Stereotact Funct Neurosurg. 1998 Oct;70 Suppl 1:110-8.

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

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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.

Mod Pathol. 1998 Jun;11(6):579-84.

Primary fibrosarcoma of the sella unrelated to previous radiation therapy.

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Fibrosarcomas involving the sella turcica are rare lesions and, when encountered, have been associated with previous radiation of a pituitary adenoma. Although primary intracranial fibrosarcomas are well recognized, no case of primary fibrosarcoma of the sella turcica has been reported to date. We describe here a patient who presented with a 2-month history of headache, visual disturbances, and diabetes insipidus. Her past medical history was unremarkable, with no radiation therapy. Magnetic resonance imaging revealed a sellar/suprasellar lesion that at surgery appeared firm in consistency. A radical removal of the mass was performed through a transsphenoidal approach. The patient recovered promptly from the operation and 2 weeks later, given the aggressive histologic appearance of the lesion, underwent gamma knife radiosurgery. Seven months after diagnosis, the patient presented with local tumor recurrence. A subtotal surgical resection was performed, and additional postsurgical treatment is still under consideration. Although most often related to previous radiation of the pituitary gland, primary fibrosarcomas can occur in the sella. This possibility should be suspected in the differential diagnosis of sellar masses that lack the classical characteristics of the much more common pituitary adenomas.

Stereotact Funct Neurosurg. 1998 Oct;70 Suppl 1:95-109.

Four years' experiences in the treatment of pituitary adenomas with gamma knife radiosurgery.

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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.

Radiat Oncol Investig. 1998;6(1):26-34.

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

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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.

Childs Nerv Syst. 1997 May;13(5):250-6.

Basal interhemispheric supra- and/or infrachiasmal approaches via superomedial orbitotomy for hypothalamic lesions: preservation of hypothalamo-pituitary functions in combination treatment with radiosurgery.

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Although several approaches to the hypothalamus have been used, none is able to give full views of the hypothalamus. The risk of permanent morbidity for hypothalamo-pituitary functions is still high, especially in patients with craniopharyngioma. Basal interhemispheric supra-chiasmal or infra-chiasmal approaches via superomedial orbitotomy were developed for better visualization of the hypothalamus. Operative techniques and results, including combination treatment with radiosurgery, are reported. Twelve patients with tumors compressing the hypothalamus upward or extending into the III ventricle, or both, were operated on: 3 tumors were removed totally, 6 tumors subtotally and 3 tumors partially. Six patients received radiosurgery for residual tumor. Four patients with hypopituitarism preoperatively required oral corticosteroids and thyroid hormones postoperatively. The basal interhemispheric approach via superomedial orbitotomy is useful for better visualization of the hypothalamus and preservation of hypothalamo-pituitary functions.

Zhongguo Zhongliu Linchuang.1996;23(6):386-389. Epub

The experience of treating pituitary adenomas using gamma knife

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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.

Yonsei Med J. 1996 Jun;37(3):165-73.

Gamma knife surgery in pituitary microadenomas.

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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.

Metabolism. 1996 Aug;45(8 Suppl 1):111-4.

Stereotactic radiosurgery of pituitary adenomas.

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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 stereotactic targeting and dose planning.

Cas Lek Cesk. 1995 Sep 6;134(17):539-42.

[Use of the radiosurgery knife in the treatment of hypophyseal adenomas].

[Article in Czech]

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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.

Acta Neurochir (Wien). 1995;134(3-4):159-66.

Failure in management of pituitary tumors discussion of 3 cases.

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Three patients with pituitary adenomas (ACTH-secreting, non-secretory, and multi-secretory) with unfavorable course, in spite of repeated microsurgery, drug therapy, as well as radiotherapy and radiosurgery, are presented. Each case was re-evaluated for possible flaws in management. Two of the invasive tumors continued to grow, in spite of correct management. The third patient with a pituitary adenoma underwent microsurgical resection, and later following a false positive finding of recurrence, received radiotherapy and underwent radiosurgery. The lesion actually was chronic inflammatory tissue.

Cas Lek Cesk. 1995 Sep 6;134(17):543-6.

[Initial experience of an endocrinologist with the treatment of hypophyseal adenomas with the Leksell gamma knife].

[Article in Czech]

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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 thyroliberin 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.

Stereotact Funct Neurosurg. 1995;64 Suppl 1:3-10.

Gamma Knife treatment of pituitary adenomas.

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Acta Neurochir Suppl. 1994;62:33-8.

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

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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.

Neurosurg Clin N Am. 1992 Jan;3(1):207-18.

Gamma knife surgery for sellar and suprasellar tumors.

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1Department of Neurological Surgery, University of Pittsburgh School of Medicine, Pennsylvania.

Recent advances in neuroimaging, coupled with stereotactic delivery of ionizing radiation, permit precise, single-treatment irradiation of various intracranial tumors. This article describes the authors' experience with the 201-source 60Co gamma knife. Initial results indicate a potential therapeutic role for radiosurgery in controlling tumor growth and hormone hypersecretion in most patients. The authors believe that radiosurgery should be considered for small pituitary adenomas when prior microsurgery has failed to control tumor growth. Radiosurgery is a primary treatment alternative for patients who are elderly, medically infirm, or refuse microsurgical removal. Further follow-up is necessary to evaluate the long-term tumor control rate, hormonal effects, and tolerance of surrounding critical structures to stereotactic radiosurgery.

Journal of neurology neurosurgery and psychiatry.1983;46(9):797-803. Epub

Stereotactic radiosurgery

Leksell, L.

The development and scope of stereotactic radiosurgery is described. The technique, which combines well with the latest diagnostic methods, has already proved a safe and effective way of treating inaccessible cerebral lesions and in particular small arteriovenous malformations, acoustic neuroma and the solid component of craniopharyngioma, as well as playing an increasingly useful role in the therapy of pituitary adenoma.