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BIBLIOGRAPHY

Leksell Gamma Knife® Radiosurgery Bibliography

Pituitary Adenoma

2012–2020

≥ 30 patient cohorts

Includes Gamma Knife-focused abstracts posted to PubMed during 2012 to 2020

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2020

[1] Gamma Knife radiosurgery for acromegaly: evaluating the role of the biological effective dose associated with endocrine remission in a series of 42 consecutive cases.

Clin Endocrinol (Oxf). 2020 Sep 28.

Balossier A, Tuleasca C, Cortet-Rudelli C, Soto-Ares G, Levivier M, Assaker R, Reyns N

PMID: 32984972 DOI: 10.1111/cen.14346

INTRODUCTION: Stereotactic radiosurgery (SRS) is a valuable treatment option for persistent and/or recurrent acromegaly secondary to growth hormone (GH) secreting pituitary adenoma (PA). Here, we assess the role of biological effective dose (BED) received by PA treated with SRS in relation with endocrine remission. **METHODS:** Forty-two patients (minimum 6 months follow-up) were included. Mean marginal dose was 27.7 (median 28, 20-35) and mean BED received by tumor was 193.1 Gy2.47 (median 199.7, 64.1-237.1). Based on the median values, we divided the patients in high tumor BED group (H-BEDtm, 199.7-237.1 Gy2.47, n=12) and low BED one (L- BEDtm, 64.1-199.7 Gy2.47 , n=10). The two groups did not differ by pretherapeutic IGF-1 levels (p=0.1) or by the prescribed dose (p=0.6). **RESULTS:** Mean follow-up period was 62.5 months (median 60.5, 9-127). Probability of IGF-1 normalization was 65% at 3 years and 72.4% at 4 years, remaining stable until last follow-up. Twenty-two (52.4%) patients had complete endocrine remission in absence of any Somatostatin analogues. Actuarial rates were 33% at 3 years and 57.4% at 7 years, further remaining stable during follow-up course. In univariate analysis, only statistically significant parameter was pretherapeutic serum IGF-1 and IGF-1 index (p=0.01). Five patients (5/26, 19.3%) without previous hypopituitarism developed new pituitary insufficiency. H-BEDtm was associated with higher rates of endocrine remission compared with L-BEDtm, with actuarial probability of 70.2% versus 48.2% at 9 years, although this did not reach statistical significance (p>0.05). **CONCLUSION:** Our study confirms that SRS by Gamma Knife is safe and effective for GH secreting PA. Pretherapeutic serum levels of IGF-1 were only statistically significant parameter for endocrine remission.

[2] Long-term results of Gamma Knife Radiosurgery for Postsurgical residual or recurrent nonfunctioning Pituitary Adenomas.

Int J Med Sci. 2020 Jun 18;17(11):1532-1540.

Deng Y, Li Y, Li X, Wu L, Quan T, Peng C, Fu J, Yang X, Yu J

PMID: 32669956 DOI: 10.7150/ijms.47168

INTRODUCTION: The aim of this retrospective study was to analyze the long-term outcomes and factors associated with treatment failure of Gamma Knife radiosurgery (GKRS) for postsurgical residual or recurrent nonfunctioning pituitary adenomas (NFPAs). **DESIGN AND METHODS:** A total of 148 cases of postsurgical residual or recurrent NFPA patients were enrolled in the study. There were 111 cases with residual tumor and 37 cases with recurrent tumor. The median age was 46.0 years (Range: 10.9-75.8 years). The median tumor volume at GKRS was 3.6 cm(3) (Range: 0.3-74.5 cm(3)), and the median tumor margin dose was 14.0 Gy (Range: 9 - 20 Gy). **RESULTS:** Tumor shrunk in 111 patients (75%), remained stable in 17 patients (11.5%), and progressed in 20 patients (13.5%) during a median of 64.5 months (Range: 14.5 - 236.0 months) of imaging follow-up. The progression-free survival rates were 99%, 91%, 88% and 74% at 1, 3, 5 and 10 years after GKRS, respectively. In a multivariate analysis, tumor margin dose (<13 Gy) was significantly associated with tumor progression (hazard ratio=3.526, 95% confidence interval=1.400-8.877, p=0.007). New hypopituitarism occurred in 22 out of 80 patients (27.5%), including hypogonadism (n=7), hypothyroidism (n=9), hypocortisolism (n=15) and growth hormone deficiency (n=1). In univariate and multivariate analysis, there were no factors significantly associated with new hypopituitarism. Six patients (4.1%) developed new or worsening visual dysfunction. Four patients (2.7%) developed new cranial neuropathy. **CONCLUSION:** In this study, GKRS can offer a high tumor control rate as well as a low rate of complications in postsurgical residual or recurrent NFPA patients.

[3] Radiosurgical Management of Patients With Persistent or Recurrent Cushing Disease After Prior Transsphenoidal Surgery: A Management Algorithm Based on a 25-Year Experience.

Neurosurgery. 2020 Apr 1;86(4):557-564.

Hughes JD, Young WF, Chang AY, Link MJ, Garces YI, Laack NN, Thompson GB, Pollock BE

PMID: 31140563 DOI: 10.1093/neuros/nyz159

BACKGROUND: Patients with persistent or recurrent Cushing disease (CD) after prior transsphenoidal surgery require further treatment to reduce the disease's metabolic consequences. **OBJECTIVE:** To assess patient outcomes after stereotactic radiosurgery (SRS) for persistent or recurrent CD from adrenocorticotropin hormone (ACTH)-secreting pituitary adenomas and propose a management algorithm. **METHODS:** Retrospective review of 38 patients without prior radiation treatment having SRS for ACTH-secreting pituitary adenomas from 1990 to 2015. Favorable outcome was defined as biochemical remission and tumor growth control. Patients were evaluated separately if they underwent bilateral adrenalectomy (Adx). **RESULTS:** Twenty patients (53%) were treated with Adx and SRS (median margin dose, 25 Gy) and 18 patients (47%) received SRS alone (median margin dose, 22.5 Gy). Median follow-up after SRS was 76 mo. Of patients undergoing Adx, 18/20 (90%) had a favorable outcome. Two patients (10%) had tumor growth requiring additional treatment. A favorable outcome was achieved in 13/18 patients (72%) having SRS alone (median, 14 mo; interquartile range, 8-23). Five patients (28%) required additional treatment due to persistent hypercortisolemia (n = 4) or hypercortisolemia and tumor growth (n = 1). Favorable outcomes were more frequent in the Adx and SRS group at 1 yr (100% vs 33%; P < .001) and 3 yr (100% vs 62%; P < .01), but no different at 5 yr (88% vs 77%; P = .63). **CONCLUSION:** SRS was effective for patients with persistent or recurrent CD. Patients with mild to moderate CD can be safely managed with SRS alone; patients with severe CD should be considered for Adx with either concurrent SRS or SRS performed at a later date if tumor growth occurs.

2019

[4] Whole Sella vs Targeted Stereotactic Radiosurgery for Acromegaly: A Multicenter Matched Cohort Study.

Neurosurgery. 2019;86(5):656-664

Taylor DG, Janssen A, Ding D, Xu Z, Mehta GU, Liscak R, Kano H, Kosak M, Martinez-Moreno N, Hobbs L, Chen CJ, Grills IS, Mathieu D, Lunsford LD, Vance ML, Sheehan JP

PMID: 31384920 DOI: 10.1093/neuros/nyz245

BACKGROUND: Targeted stereotactic radiosurgery (SRS) with sparing of the residual pituitary is the traditional radiosurgical method for pituitary adenomas. Whole-sella SRS is an alternative choice for radiologically indeterminate or large adenomas, the safety and efficacy of which has yet to be determined. **OBJECTIVE:** To determine if whole-sella SRS in acromegaly would have comparable radiographic and biochemical control to targeted SRS. We performed a multicenter, retrospective matched cohort study to compare outcomes between groups. **METHODS:** We conducted a retrospective review of acromegalic patients who underwent SRS from 1990 to 2016 at 10 centers participating in the International Radiosurgery Research Foundation. Whole-sella and targeted SRS patients were then matched in a 1:1 ratio. **RESULTS:** A total of 128 patients were eligible for inclusion. Whole-sella patients had a higher pre-SRS random serum growth hormone, larger treatment volume, and higher maximum point dose to the optic apparatus. The rates of initial/durable endocrine remission, new loss of pituitary function, and new cranial neuropathy were similar between groups. Mortality and new visual deficit were higher in the whole-sella cohort, though not statistically significant. **CONCLUSION:** There was no difference in biochemical remission or recurrence between treatment groups. Although not statistically significant, the higher rates of tumor regression and lower rates of mortality and

new visual deficit may suggest consideration of targeted SRS over whole-sella SRS in acromegaly treatment. Further research is needed to determine the association between visual deficits and mortality with whole-sella SRS.

[5] Safety and efficacy of repeat radiosurgery for acromegaly: an International Multi-Institutional Study.

Journal of neuro-oncology. 2019;145(2):301-307
Alonso CE, Bunevicius A, Trifiletti DM, Larner J, Lee CC, Pai FY, Liscak R, Kosak M, Kano H, Sisterson ND, Mathieu D, Lunsford LD, Sheehan JP
PMID: 31541405 DOI: 10.1007/s11060-019-03296-8
PURPOSE: Surgical resection is the first line treatment for growth hormone (GH) secreting tumors. Stereotactic radiosurgery (SRS) is recommended for patients who do not achieve endocrine remission after resection. The purpose of this study was to evaluate safety and efficacy of repeat radiosurgery for acromegaly. **METHODS:** Three hundred and ninety-eight patients with acromegaly treated with the Gamma Knife radiosurgery (Elekta AB, Stockholm) were identified from the International Gamma Knife Research Foundation database. Among these, 21 patients underwent repeated SRS with sufficient endocrine follow-up and 18 patients had sufficient imaging follow-up. Tumor control was defined as lack of adenoma progression on imaging. Endocrine remission was defined as a normal IGF-1 concentration while off medical therapy. **RESULTS:** Median time from initial SRS to repeat SRS was 5.0 years. The median imaging and endocrine follow-up duration after repeat SRS was 3.4 and 3.8 years, respectively. The median initial marginal dose was 17 Gy, and the median repeat marginal dose was 23 Gy. Of the 18 patients with adequate imaging follow up, 15 (83.3%) patients had tumor control and of 21 patients with endocrine follow-up, 9 (42.9%) patients had endocrine remission at last follow-up visit. Four patients (19.0%) developed new deficits after repeat radiosurgery. Of these, 3 patients had neurologic deficits and 1 patient had endocrine deficit. **CONCLUSIONS:** Repeat radiosurgery for persistent acromegaly offers a reasonable benefit to risk profile for this challenging patient cohort. Further studies are needed to identify patients best suited for this type of approach.

[6] Toxicity Profiles of Fractionated Radiotherapy, Contemporary Stereotactic Radiosurgery, and Transsphenoidal Surgery in Nonfunctioning Pituitary Macroadenomas.

Cancers. 2019;11(11)
Chang CL, Yuan KS, Wu ATH, Wu SY
PMID: 31717774 DOI: 10.3390/cancers11111658
BACKGROUND: Here, we compared the toxicity profiles of contemporary stereotactic radiosurgery (SRS), modern fractionated radiotherapy (FRT), and transsphenoidal surgery used to treat nonfunctioning pituitary macroadenomas. **METHODS:** We included the data of patients with nonfunctioning pituitary macroadenomas. To compare treatment outcomes, the patients were categorized groups 1 (those receiving modern FRT), 2 (those receiving contemporary SRS), and 3 (those receiving transsphenoidal surgery). The multivariable Cox proportional hazards regression analysis was performed to yielded adjusted hazard ratios (aHRs) and their 95% CIs for local recurrence in groups 2 and 3 compared with group 1. **RESULTS:** We included the data of 248 patients with nonfunctioning pituitary macroadenomas. The analytical results revealed no significant differences in second primary brain or head and neck cancer, hypopituitarism, or optic nerve injury between the three cohorts. The multivariable Cox proportional hazards regression analysis revealed that compared with group 1, the aHRs (95% CIs) for stroke risk in groups 2 and 3 were 0.37 (0.14-0.99) and 0.51 (0.31-0.84), respectively. **CONCLUSION:** Contemporary SRS and transsphenoidal surgery for nonfunctioning pituitary macroadenoma treatment have equivalent toxicity profiles. However, modern FRT for nonfunctioning pituitary macroadenoma treatment might considerably increase stroke risk.

[7] The benefit and risk of stereotactic radiosurgery for prolactinomas: an international multicenter cohort study.

Journal of neurosurgery. 2019;:1-10
Hung YC, Lee CC, Yang HC, Mohammed N, Kearns KN, Nabeel AM, Abdel Karim K, Emad Eldin RM, El-Shehaby AMN, Reda WA, Tawadros SR, Liscak R, Jezkova J, Lunsford LD, Kano H, Sisterson ND, Martinez Alvarez R, Martinez Moreno NE, Kondziolka D, Golfinos JG, Grills I, Thompson A, Borghei-Razavi H, Maiti TK, Barnett GH, McInerney J, Zacharia BE, Xu Z, Sheehan JP
PMID: 31374549 DOI: 10.3171/2019.4.JNS183443
OBJECTIVE: The most common functioning pituitary adenoma is prolactinoma. Patients with medically refractory or residual/recurrent tumors that are not amenable to resection can be treated with stereotactic radiosurgery (SRS). The aim of this multicenter study was to evaluate the role of SRS for treating prolactinomas. **METHODS:** This retrospective study included prolactinomas treated with SRS between 1997 and 2016 at ten institutions. Patients' clinical and treatment parameters were investigated. Patients were considered to be in endocrine remission when they had a normal level of prolactin (PRL) without requiring dopamine agonist medications. Endocrine control was defined as endocrine remission or a controlled PRL level </= 30 ng/ml with dopamine agonist therapy. Other outcomes were evaluated including new-onset hormone deficiency, tumor recurrence, and new neurological complications. **RESULTS:** The study cohort comprised 289 patients. The endocrine remission rates were 28%, 41%, and 54% at 3, 5, and 8 years after SRS, respectively. Following SRS, 25% of patients (72/289) had new hormone deficiency. Sixty-three percent of the patients (127/201) with available data attained endocrine control. Three percent of patients (9/269) had a new visual complication after SRS. Five percent of the patients (13/285) were recorded as having tumor progression. A pretreatment PRL level </= 270 ng/ml was a predictor of endocrine remission (p = 0.005, adjusted HR 0.487). An increasing margin dose resulted in better endocrine control after SRS (p = 0.033, adjusted OR 1.087). **CONCLUSIONS:** In patients with medically refractory prolactinomas or a residual/recurrent prolactinoma, SRS affords remarkable therapeutic effects in endocrine remission, endocrine control, and tumor control. New-onset hypopituitarism is the most common adverse event.

[8] Gamma Knife radiosurgery for the treatment of Nelson's syndrome: a multicenter, international study.

Journal of neurosurgery. 2019;:1-6
Cordeiro D, Xu Z, Li CE, Iorio-Morin C, Mathieu D, Sisterson ND, Kano H, Attuati L, Picozzi P, Sheehan KA, Lee CC, Liscak R, Jezkova J, Lunsford LD, Sheehan J
PMID: 31299652 DOI: 10.3171/2019.4.JNS19273
OBJECTIVE: Nelson's syndrome is a rare and challenging neuroendocrine disorder, and it is associated with elevated adrenocorticotrophic hormone (ACTH) level, skin hyperpigmentation, and pituitary adenoma growth. Management options including resection and medical therapy are traditional approaches. Ionizing radiation in the form of Gamma Knife radiosurgery (GKRS) is also being utilized to treat Nelson's syndrome. In the current study the authors sought to better define the therapeutic role of stereotactic radiosurgery (SRS) in Nelson's syndrome. **METHODS:** Study patients with Nelson's syndrome were treated with single-fraction GKRS (median margin dose of 25 Gy) at 6 different centers as part of an International Radiosurgery Research Foundation (IRRF) investigation. Data including neurological function, endocrine response, and radiological tumor response were collected and sent to the study-coordinating center for review. Fifty-one patients with median endocrine and radiological follow-ups of 91 and 80.5 months from GKRS, respectively, were analyzed for endocrine remission, tumor control, and neurological outcome. Statistical methods were used to identify prognostic factors for these endpoints. **RESULTS:** At last follow-up, radiological tumor control was achieved in 92.15% of patients. Endocrine remission off medical management and reduction in pre-SRS ACTH level were achieved in 29.4% and 62.7% of patients, respectively. Improved remission rates were associated with a shorter time interval between resection and GKRS (p = 0.039). Hypopituitarism was seen in 21.6% and new visual deficits were

demonstrated in 15.7% of patients. **CONCLUSIONS:** GKRS affords a high rate of pituitary adenoma control and improvement in ACTH level for the majority of Nelson's syndrome patients. Hypopituitarism is the most common adverse effect from GKRS in Nelson's syndrome patients and warrants longitudinal follow-up for detection and endocrine replacement.

[9] Low-Dose Gamma Knife Radiosurgery for Acromegaly.
Neurosurgery. 2019;85(1):E20-E30
Pai FY, Chen CJ, Wang WH, Yang HC, Lin CJ, Wu HM, Lin YC, Chen HS, Yen YS, Chung WY, Guo WY, Pan DH, Shiau CY, Lee CC
PMID: 30169716 DOI: 10.1093/neuros/nyy410
BACKGROUND: Remission rate is associated with higher dose of Gamma Knife Radiosurgery (GKRS; Gamma Knife: Elekta AB, Stockholm, Sweden) for acromegaly, but the dose >/=25 Gy is not always feasible when the functioning adenoma is close to optic apparatus. **OBJECTIVE:** To evaluate the efficacy and safety of low-dose (<25 Gy) GKRS in the treatment of patients with acromegaly. **METHODS:** Single-center retrospective review of acromegaly cases treated with GKRS between June 1994 and December 2016. A total of 76 patients with the diagnosis of acromegaly who were treated with low-dose GKRS were selected for inclusion. Patients were treated with a median margin dose, isodose line, and treatment volume of 15.8 Gy, 57.5%, and 4.8 mL, respectively. Any identifiable portion of the optic apparatus was limited to a radiation dose of 10 Gy. All patients underwent full endocrine, ophthalmological, and imaging evaluation prior to and after GKRS treatments, and results of these were analyzed. **RESULTS:** Biochemical remission was achieved in 33 (43.4%) patients. Actuarial remission rates were 20.3%, 49.9%, and 76.3% at 4, 8, and 12 yr, respectively. Absence of cavernous sinus invasion (P = .042) and lower baseline insulin-like growth factor-1 levels (P = .019) were significant predictors of remission. New hormone deficiencies were found in 9 (11.8%) patients. Actuarial hormone deficiency rates were 3%, 14%, and 22.2% at 4, 8, and 10 yr, respectively. Two (2.6%) patients who achieved initial remission experienced recurrence. No optic complications were encountered. **CONCLUSION:** Reasonable remission and new hormone deficiency rates can be achieved with low-dose GKRS for acromegaly. These rates may be comparable to those with standard GKRS margin doses.

[10] Outcomes After Gamma Knife Stereotactic Radiosurgery in Pediatric Patients with Cushing Disease or Acromegaly: A Multi-Institutional Study.
World neurosurgery. 2019;125:e1104-e1113
Shrivastava A, Mohammed N, Xu Z, Liscak R, Kosak M, Krsek M, Karim KA, Lee CC, Martinez-Moreno N, Lee Vance M, Lunsford LD, Sheehan JP
PMID: 30790739 DOI: 10.1016/j.wneu.2019.01.252
OBJECTIVE: Pituitary adenomas comprise about 3% of all intracranial tumors in pediatric patients. This study examines the role of stereotactic radiosurgery in the management of pediatric acromegaly or patients with Cushing disease (CD). **METHODS:** From an international consortium, we retrospectively collected treatment and outcome data on pediatric adrenocorticotrophic hormone and growth hormone-secreting pituitary adenomas treated with Gamma Knife radiosurgery (GKRS). There were a total of 36 patients including 24 with CD and 12 with acromegaly. The data were analyzed to assess outcomes including tumor control, endocrine remission, and adverse effects. Statistical analysis was performed to determine correlation between clinical/treatment parameters and outcomes. **RESULTS:** At the last follow-up after GKRS, endocrine remission rates for CD and acromegaly were 80% and 42%, respectively. Tumor control was achieved in 87.5% of patients with CD and in 42% of patients with acromegaly. New pituitary hormone deficiency occurred in 7 of the 36 patients at a median time of 18 months after GKRS (range, 12-81 months). The predictive factors for endocrine remission were age <15 years (P = 0.015) and margin dose (P = 0.042). The median endocrine follow-up was 63.7 months (range, 7-246 months). **CONCLUSIONS:** GKRS affords reasonable rates of endocrine remission and tumor control in most pediatric patients with functioning adenomas. The most common post-GKRS complication was hypopituitarism, although this occurred in only a few patients. Given the larger at-risk period for pediatric patients, further study is required to evaluate for delayed recurrences and hypopituitarism.

[11] Primary versus postoperative stereotactic radiosurgery for acromegaly: a multicenter matched cohort study.
Journal of neurosurgery. 2019;:1-10
Mohammed N, Ding D, Hung YC, Xu Z, Lee CC, Kano H, Martinez-Alvarez R, Martinez-Moreno N, Mathieu D, Kosak M, Cifarelli CP, Katsevman GA, Lunsford LD, Lee Vance M, Sheehan JP
PMID: 31026829 DOI: 10.3171/2019.1.JNS183398
OBJECTIVE: The role of primary stereotactic radiosurgery (SRS) in patients with medically refractory acromegaly who are not operative candidates or who refuse resection is poorly understood. The aim of this multicenter, matched cohort study was to compare the outcomes of primary versus postoperative SRS for acromegaly. **METHODS:** The authors reviewed an International Radiosurgery Research Foundation database of 398 patients with acromegaly who underwent SRS and categorized them into primary or postoperative cohorts. Patients in the primary SRS cohort were matched, in a 1:2 ratio, to those in the postoperative SRS cohort, and the outcomes of the 2 matched cohorts were compared. **RESULTS:** The study cohort comprised 78 patients (median follow-up 66.4 months), including 26 and 52 in the matched primary and postoperative SRS cohorts, respectively. In the primary SRS cohort, the actuarial endocrine remission rates at 2 and 5 years were 20% and 42%, respectively. The Cox proportional hazards model showed that a lower pre-SRS insulin-like growth factor-1 level was predictive of initial endocrine remission (p = 0.03), whereas a lower SRS margin dose was predictive of biochemical recurrence after initial remission (p = 0.01). There were no differences in the rates of radiological tumor control (p = 0.34), initial endocrine remission (p = 0.23), biochemical recurrence after initial remission (p = 0.33), recurrence-free survival (p = 0.32), or hypopituitarism (p = 0.67) between the 2 matched cohorts. **CONCLUSIONS:** Primary SRS has a reasonable benefit-to-risk profile for patients with acromegaly in whom resection is not possible, and it has similar outcomes to endocrinologically comparable patients who undergo postoperative SRS. SRS with medical therapy in the latent period can be used as an alternative to surgery in selected patients who cannot or do not wish to undergo resection.

[12] Results of Treatment with Modern Fractionated Radiotherapy, Contemporary Stereotactic Radiosurgery, and Transsphenoidal Surgery in Nonfunctioning Pituitary Macroadenoma.
Journal of clinical medicine. 2019;8(4)
Hsiao PK, Chang CL, Yuan KS, Wu ATH, Wu SY
PMID: 30995734 DOI: 10.3390/jcm8040518
BACKGROUND: To compare the effects of contemporary stereotactic radiosurgery (SRS), modern fractionated radiotherapy (FRT), and transsphenoidal surgery on nonfunctioning pituitary macroadenoma. **METHODS:** We enrolled patients with nonfunctioning pituitary macroadenoma. To compare treatment outcomes, the patients were categorized into three groups according to the treatment modality: group 1, patients receiving modern FRT; group 2, patients receiving contemporary SRS; and group 3, patients receiving transsphenoidal surgery. **RESULTS:** In total, 548 patients with nonfunctioning pituitary macroadenoma were selected for our study. Univariate and multivariate Cox regression analysis results indicated that the treatment modalities were significant independent prognostic factors. In multivariable Cox proportional hazard regression analysis, the adjusted hazard ratios (aHR; 95% confidence interval (CI)) of local recurrence were 0.27 (0.10-0.91) and 1.95 (1.25-2.37) for the SRS and transsphenoidal surgery cohorts, respectively, in comparison with the FRT cohort. The aHR (95% CI) of all-cause mortality was 1.03 (0.68-1.56) for the transsphenoidal surgery cohort in comparison with the FRT cohort, without statistical significance. However, the aHR (95% CI) of all-cause mortality was 0.36 (0.15-0.85) for the SRS cohort in comparison with the FRT cohort. **CONCLUSION:** Contemporary SRS has optimal effects on local recurrence and survival compared with modern FRT and transsphenoidal surgery. Modern FRT is associated with more favorable local control and equal survival compared with transsphenoidal surgery.

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[13] Radiation dose to neuroanatomical structures of pituitary adenomas and the effect of Gamma Knife radiosurgery on pituitary function.

Journal of neurosurgery. 2019;:1-8

Pomeraniec IJ, Taylor DG, Cohen-Inbar O, Xu Z, Lee Vance M, Sheehan JP

PMID: 30978685 DOI: 10.3171/2019.1.JNS182296

OBJECTIVE: Gamma Knife radiosurgery (GKRS) provides a safe and effective management option for patients with all types of pituitary adenomas. The long-term adverse effects of targeted radiation to the hypothalamic-pituitary axis in relationship to radiation dose remain unclear. In this retrospective review, the authors investigated the role of differential radiation doses in predicting long-term clinical outcomes and pituitary function after GKRS for pituitary adenomas. **METHODS:** A cohort of 236 patients with pituitary tumors (41.5% nonfunctioning, 58.5% functioning adenomas) was treated with GKRS between 1998 and 2015. Point dosimetric measurements, with no minimum volume, to 14 consistent points along the hypothalamus bilaterally, pituitary stalk, and normal pituitary were made. Statistical analyses were performed to determine the impact of doses to critical structures on clinical, radiological, and endocrine outcomes. **RESULTS:** With a median follow-up duration of 42.9 months, 18.6% of patients developed new loss of pituitary function. The median time to endocrinopathy was 21 months (range 2-157 months). The median dose was 2.1 Gy to the hypothalamus, 9.1 Gy to the pituitary stalk, and 15.3 Gy to the normal pituitary. Increasing age ($p = 0.015$, HR 0.98) and ratio of maximum dose to the pituitary stalk over the normal pituitary gland ($p = 0.013$, HR 0.22) were independent predictors of new or worsening hypopituitarism in the multivariate analysis. Sex, margin dose, treatment volume, nonfunctioning adenoma status, or ratio between doses to the pituitary stalk and hypothalamus were not significant predictors. **CONCLUSIONS:** GKRS offers a low rate of delayed pituitary insufficiency for pituitary adenomas. Doses to the hypothalamus are low and generally do not portend endocrine deficits. Patients who are treated with a high dose to the pituitary stalk relative to the normal gland are at higher risk of post-GKRS endocrinopathy. Point dosimetry to specific neuroanatomical structures revealed that a ratio of stalk-to-gland radiation dose of 0.8 or more significantly increased the risk of endocrinopathy following GKRS. Improvement in the gradient index toward the stalk and normal gland may help preserve endocrine function.

[14] Empirical versus progression-guided stereotactic radiosurgery for non-functional pituitary macroadenomas after subtotal resection.

Journal of neuro-oncology. 2019;142(2):291-297

Lee CC, Yang HC, Chen CJ, Lin CJ, Wu HM, Chung WY, Shiau CY, Guo WY, Pan DH

PMID: 30635763 DOI: 10.1007/s11060-019-03095-1

OBJECTIVE: There is a lack of consensus regarding whether if residual non-functional macroadenomas (NFM) should undergo empirical stereotactic radiosurgery (SRS) or be monitored until tumor progression before SRS treatment. The aim of this study is to compare the risks and benefits of empirical versus progression-guided SRS for NFM after subtotal resection. **METHODS:** This is a retrospective study of consecutive NFM patients who subtotal surgical resection followed by SRS between 1999 and 2014. Patients were dichotomized into two groups: empirical SRS (SRS without evidence of tumor progression) and progression-guided SRS (SRS after demonstration of tumor progression) groups. Tumor response was categorized into: (1) regression, >/= 10% decrease in tumor volume; (2) stable, < 10% increase or decrease in tumor volume; and (3) progression, >/= 10% increase in tumor volume. Tumor control comprised stable tumor response and tumor regression. **RESULTS:** Of the 112 patients who underwent SRS for NFM, 106 patients were treated for residual NFM after surgical resection, and included in the final analysis. The empirical SRS and progression-guided SRS groups comprised 46 and 60 patients, respectively. Overall tumor control rate was 88.7%. Higher rate of tumor control was achieved in the empirical SRS group compared to the progression-guided SRS group (95.65% vs. 83.33%, $p = 0.047$). Rates of new visual field deficit, cranial neuropathy and endocrinopathy were comparable between the two groups. Empirical SRS group had higher rates of progression-free survival compared to progression-guided SRS group ($p = 0.015$). Actuarial progression-free survival rates for the empirical SRS group were 93.2%, 93.2%, and 81.5% at 3, 5, and 10 years after SRS. Actuarial progression-free survival rates for the progression-guided SRS were 86.4%, 82.1%, and 68.4% at 3, 5, and 10 years after SRS. **CONCLUSION:** Empirical SRS offers higher rates of tumor control and progression-free survival compared to progression-guided SRS in patients with residual NFM after surgical resection. Rates of new hypopituitarism and cranial neuropathies were comparable between the two groups.

[15] Stereotactic Radiosurgery for Acromegaly: An International Multicenter Retrospective Cohort Study.

Neurosurgery. 2019;84(3):717-725

Ding D, Mehta GU, Patibandla MR, Lee CC, Liscak R, Kano H, Pai FY, Kosak M, Sisterson ND, Martinez-Alvarez R, Martinez-Moreno N, Mathieu D, Grills IS, Blas K, Lee K, Cifarelli CP, Katsevman GA, Lee JYK, McShane B, Kondziolka D, Lunsford LD, Vance ML, Sheehan JP

PMID: 29757421 DOI: 10.1093/neuros/nyy178

BACKGROUND: Stereotactic radiosurgery (SRS) is a treatment option for persistent or recurrent acromegaly secondary to a growth hormone secreting pituitary adenoma, but its efficacy is inadequately defined. **OBJECTIVE:** To assess, in a multicenter, retrospective cohort study, the outcomes of SRS for acromegaly and determine predictors. **METHODS:** We pooled and analyzed data from 10 participating institutions of the International Gamma Knife Research Foundation for patients with acromegaly who underwent SRS with endocrine follow-up of >/=6 mo. **RESULTS:** The study cohort comprised 371 patients with a mean endocrine follow-up of 79 mo. IGF-1 lowering medications were held in 56% of patients who were on pre-SRS medical therapy. The mean SRS treatment volume and margin dose were 3.0 cm3 and 24.2 Gy, respectively. The actuarial rates of initial and durable endocrine remission at 10 yr were 69% and 59%, respectively. The mean time to durable remission after SRS was 38 mo. Biochemical relapse after initial remission occurred in 9%, with a mean time to recurrence of 17 mo. Cessation of IGF-1 lowering medication prior to SRS was the only independent predictor of durable remission ($P = .01$). Adverse radiation effects included the development of >/=1 new endocrinopathy in 26% and >/=1 cranial neuropathy in 4%. **CONCLUSION:** SRS is a definitive treatment option for patients with persistent or recurrent acromegaly after surgical resection. There appears to be a statistical association between the cessation of IGF-1 lowering medications prior to SRS and durable remission.

[16] The role of Crooke's changes in recurrence and remission after gamma knife radiosurgery.

Journal of neuro-oncology. 2019;142(1):171-181

Cordeiro D, Xu Z, Nasser M, Lopes B, Vance ML, Sheehan J

PMID: 30607704 DOI: 10.1007/s11060-018-03078-8

PURPOSE: The objective of this study is to evaluate the role of Crooke's changes (CC) in normal the peri-tumoral anterior pituitary gland, in patients with Cushing's disease (CD) with a histopathological confirmed corticotroph adenoma, and determine if there is any difference in the recurrence and remission rates in CD patients after treatment with Gamma Knife Radiosurgery (GKRS). **METHODS:** All patients treated with GKRS for CD from 2005 to 2016 at our institution were identified. Patients had a confirmed adrenocorticotropic (ACTH)-secreting adenoma, i.e. corticotroph adenoma, and normal pituitary gland included in the surgical specimen, and specimens were stained with hematoxylin and eosin and also immunostaining for cytokeratin and ACTH. Statistical analyses were performed in a total of 61 patients who met the inclusion criteria. Additionally, we analyzed 20 patients in each group, with and without CC, after they were matched in a propensity score fashion. **RESULTS:** Endocrine remission defined as, a normal 24 h urine free cortisol while off suppressive medication, occurred in 48 patients (78.7%), with 76.9% in those with CC and 81.8% in those without CC. There was no statistical significant difference between the two groups in regarding remission

(p = 0.312) or recurrence (p = 0.659) in either the unmatched or matched cohorts. **CONCLUSION:** The presence or absence of CC in normal pituitary gland does not appear to confer a lower rate of remission or a higher rate of recurrence after GKRS. Patients with pituitary corticotroph adenomas that present with CC features may be well served by Stereotactic radiosurgery (SRS).

[17] Safety and efficacy of multisession gamma knife radiosurgery for residual or recurrent pituitary adenomas.
Endocrine. 2019 Feb 23. pii: 10.1007/s12020-019-01876-2.
Albano L, Losa M, Nadin F, Barzaghi LR, Parisi V, Del Vecchio A, Bolognesi A, Mortini P
PMID: 30798432 DOI: 10.1007/s12020-019-01876-2
PURPOSE: To define the efficacy and complications of multisession Gamma Knife radiosurgery (MGKRS) delivered in three consecutive sessions for the treatment of residual or recurrent pituitary adenomas (PAs). **METHODS:** This was a retrospective study of data from the Neurosurgery and Gamma Knife Radiosurgery Department at San Raffaele Hospital between May 2008 and September 2017. We recruited 47 consecutive patients undergoing MGKRS in three consecutive fractions for residual or recurrent PA with a distance from the anterior optic pathway inferior to 2-3 mm. **RESULTS:** Thirty-eight (80.8%) patients had a nonfunctioning-PA (NFPA) while 9 (19.2%) had a hormone-secreting PA (HSPA). Tumor control was achieved in 100% of patients. Tumor shrinkage was seen in 33 out of 44 (75.0%) patients with a radiological follow-up. Mean tumor volume before MGKRS was 3.93 cm(3). The mean tumor volume at last follow-up was 2.11 cm(3), with a mean tumor shrinkage of 50.2%, as compared with baseline. One case of suspected radiation-induced optic neuropathy (RION) was documented while new-onset hypopituitarism for any axis occurred in 12 of the 31 (38.7%) patients at risk. The mean follow-up was 44.6 +/- 4.0 months (range, 6-111 months). **CONCLUSIONS:** MGKRS is a valid alternative to external fractionated radiotherapy and other types of stereotactic radiosurgery for the treatment of PAs, achieving a high tumor control rate with a low risk of visual deterioration. Moreover, the majority of patients showed a significant reduction of tumor size in the long term.

[18] Long-Term Efficacy and Tolerability of Gamma Knife Radiosurgery for Growth Hormone-Secreting Adenoma: A Retrospective Multicenter Study (MERGE-001).
World neurosurgery. 2019;122:e1291-e1299
Kong DS, Kim YH, Kim YH, Hur KY, Kim JH, Kim MS, Paek SH, Kwon DH, Kim DK, Lee JI
PMID: 30448582 DOI: 10.1016/j.wneu.2018.11.038
OBJECTIVE: Little is known about the long-term efficacy, prognostic factors, and tolerability of gamma knife radiosurgery (GKS) for acromegaly. The aim of this study was to investigate long-term hormonal effects, prognostic factors, and tolerability of GKS in patients with growth hormone-secreting adenoma. **METHODS:** A retrospective multicenter study over 25 years with a median follow-up of 85.2 months was performed. A total of 138 patients from 3 tertiary referral centers in South Korea were included in this study between 1991 and 2017. Main outcome measures were endocrine remission, endocrine control under somatostatin analogues, and hypopituitarism. **RESULTS:** With a mean follow-up period of 85.2 months (range, 12-304 months), overall median time to the endocrine remission and control under long-acting somatostatin analogues was 138 months and 96 months, respectively. Female sex, normal age-adjusted insulin growth factor-1 (IGF-1) </= 2, and GKS as an adjuvant treatment were significantly favorable factors for remission (P = 0.004, P = 0.001, P = 0.010, respectively). The early response group had a significantly lower proportion of normal age-adjusted IGF-1 levels >2 than did the late response group (22.2% vs. 51.7%, P = 0.035); also, the early response group had lower radiation dose than the late response group (24.3 Gy vs. 27.0 Gy, P = 0.003). The incidence of GKS-induced hypopituitarism (1 or more) was 12 of 138 patients (8.6%) at the last follow-up. **CONCLUSIONS:** In acromegalic patients, women with normal age-adjusted IGF-1 </= 2 and GKS as an adjuvant treatment have a better response to GKS. We should take into account the variability of radiosensitivity of the tumor according to the gender and IGF-1 level.

[19] Long-Term Follow-Up Studies of Gamma Knife Radiosurgery for Postsurgical Nonfunctioning Pituitary Adenomas.
World neurosurgery. 2019;
Sun S, Liu A, Zhang Y
PMID: 30660894 DOI: 10.1016/j.wneu.2019.01.009
OBJECTIVE: The aim of this study was to evaluate the long-term clinical outcomes of Gamma Knife radiosurgery (GKRS) for residual and recurrent nonfunctioning pituitary adenomas (NFPAs) after surgery and the role of GKRS in the management of NFPAs. **METHODS:** Between January 2000 and December 2010, 204 patients with residual or recurrent NFPAs undergoing GKRS were enrolled in this study according to the inclusion criteria. The median age of the patients was 48 years (mean, 48 years; range, 14-79 years). The median tumor volume was 3.3 mL (mean, 5.2 mL; range, 0.3-26.4 mL). The median margin dose was 14 Gy (mean, 14 Gy; range, 9-18 Gy). The median maximum dose was 31 Gy (mean, 30 Gy; 20-40 Gy). The median duration of follow-up was 86 months (mean, 88 months; range, 12-213 months). **RESULTS:** Of these 204 patients, the latest follow-up magnetic resonance imaging studies showed tumor regression in 102 patients (50%), tumor stability in 81 patients (40%), and tumor enlargement in 21 patients (10%). The tumor control rate of this cohort was 90%. The cumulative progression-free survival at 3, 5, 8, 10, and 15 years was 97%, 95%, 92%, 92%, and 81%, respectively. Thirty-seven patients (18%) developed new-onset hypopituitarism, with 1 patient experiencing panhypopituitarism. Five patients (2.5%) presented with new or worsening visual dysfunction without tumor growth. No new cranial nerve dysfunction was shown and no second brain tumor was identified. **CONCLUSIONS:** GKRS provided high tumor control and a low complication rate in our long-term follow-up. We recommend that early GKRS should be considered the routine adjuvant treatment for residual NFPAs approximately 6 months after subtotal surgical resection.

2018

[20] Neurocognitive changes in pituitary adenoma patients after Gamma Knife radiosurgery.
Journal of neurosurgery. 2018;129(Suppl1):55-62
Tooze A, Sheehan JP
PMID: 30544290 DOI: 10.3171/2018.7.GKS181595
OBJECTIVE: Pituitary adenomas and the treatment required for the underlying neuropathology have frequently been associated with cognitive dysfunction. However, the mechanisms for these impairments remain the subject of much debate. The authors evaluated cognitive outcomes in patients treated with or without Gamma Knife radiosurgery (GKRS) for an underlying pituitary adenoma. **METHODS:** This was a retrospective, institutional review board-approved, single-institution study. A total of 51 patients (23 male, 28 female) treated for pituitary adenoma were included in this neurocognitive study. Twenty-one patients underwent GKRS following transsphenoidal surgery, 22 patients were treated with transsphenoidal surgery alone, and eight patients were conservatively managed or were treated with medical management alone. Comparisons using psychometric tests of general intellectual abilities, memory, and executive functions were made between the treatment groups, between male and female patients, and between patients with Cushing's disease and those with nonfunctioning adenoma (NFA). **RESULTS:** The entire patient sample, the NFA group, and the GKRS group scored significantly below expected on measures of both immediate and delayed memory, particularly for visually presented information (p </= 0.05); however, there were no significant differences between the patients with Cushing's disease and those with NFA (t </= 0.56, p >/= 0.52). In those who underwent GKRS,

memory scores were not significantly different from those in the patients who did not undergo GKRS (t </= 1.32, p >/= 0.19). Male patients across the sample were more likely to demonstrate impairments in both immediate memory (t = -3.41, p = 0.003) and delayed memory (t = -3.80, p = 0.001) than were female patients (t </= 1.09, p >/= 0.29). There were no impairments on measures of general intellectual functioning or executive functions in any patient group. The potential contributions of tumor size and hormone levels are discussed. **CONCLUSIONS:** Overall, pituitary adenoma patients demonstrated relative impairment in anterograde memory. However, GKRS did not lead to adverse effects for immediate or delayed memory in pituitary adenoma patients. Cognitive assessment of pituitary adenoma patients is important in their longitudinal care.

[21] Hypopituitarism after Gamma Knife surgery for postoperative nonfunctioning pituitary adenoma.

Journal of neurosurgery. 2018;129(Suppl1):47-54
Oh JW, Sung KS, Moon JH, Kim EH, Chang WS, Jung HH, Chang JW, Park YG, Kim SH, Chang JH
PMID: 30544293 DOI: 10.3171/2018.7.GKS181589
OBJECTIVE: This study investigated long-term follow-up data on the combined pituitary function test (CPFT) in patients who had undergone transsphenoidal surgery (TSS) for nonfunctioning pituitary adenoma (NFPA) to determine the clinical parameters indicative of hypopituitarism following postoperative Gamma Knife surgery (GKS). **METHODS:** Between 2001 and 2015, a total of 971 NFPA patients underwent TSS, and 76 of them (7.8%) underwent postoperative GKS. All 76 patients were evaluated with a CPFT before and after GKS. The hormonal states were analyzed based on the following parameters: relevant factors before GKS (age, sex, extent of resection, pre-GKS hormonal states, time interval between TSS and GKS), GKS-related factors (tumor volume; radiation dose to tumor, pituitary stalk, and normal gland; distance between tumor and stalk), and clinical outcomes (tumor control rate, changes in hormonal states, need for hormone-related medication due to hormonal changes). **RESULTS:** Of the 971 NFPA patients, 797 had gross-total resection (GTR) and 174 had subtotal resection (STR). Twenty-five GTR patients (3.1%) and 51 STR patients (29.3%) underwent GKS. The average follow-up period after GKS was 53.5 +/- 35.5 months, and the tumor control rate was 96%. Of the 76 patients who underwent GKS, 23 were excluded due to pre-GKS panhypopituitarism (22) or loss to follow-up (1). Hypopituitarism developed in 13 (24.5%) of the remaining 53 patients after GKS. A higher incidence of post-GKS hypopituitarism occurred in the patients with normal pre-GKS hormonal states (41.7%, 10/24) than in the patients with abnormal pre-GKS hormonal states (10.3%, 3/29; p = 0.024). Target tumor volume (4.7 +/- 3.9 cm3), distance between tumor and pituitary stalk (2.0 +/- 2.2 mm), stalk dose (cutoffs: mean dose 7.56 Gy, maximal dose 12.3 Gy), and normal gland dose (cutoffs: maximal dose 13.9 Gy, minimal dose 5.25 Gy) were factors predictive of post-GKS hypopituitarism (p < 0.05). **CONCLUSIONS:** This study analyzed the long-term follow-up CPFT data on hormonal changes in NFPA patients who underwent GKS after TSS. The authors propose a cutoff value for the radiation dose to the pituitary stalk and normal gland for the prevention of post-GKS hypopituitarism.

[22] Hypopituitarism after Gamma Knife radiosurgery for pituitary adenomas: a multicenter, international study

Journal of neurosurgery. 2018;
Cordeiro D, Xu Z, Mehta GU, Ding D, Vance ML, Kano H, Sisterson N, Yang HC, Kondziolka D, Lunsford LD, Mathieu D, Barnett GH, Chiang V, Lee J, Sneed P, Su YH, Lee CC, Krsek M, Liscak R, Nabeel AM, El-Shehaby A, Karim KA, Reda WA, Martinez-Moreno N, Martinez-Alvarez R, Blas K, Grills I, Lee KC, Kosak M, Cifarelli CP, Katsevman GA, Sheehan JP
PMID: 31369225 DOI: 10.3171/2018.5.JNS18509
OBJECTIVE: Recurrent or residual adenomas are frequently treated with Gamma Knife radiosurgery (GKRS). The most common complication after GKRS for pituitary adenomas is hypopituitarism. In the current study, the authors detail the timing and types of hypopituitarism in a multicenter, international cohort of pituitary adenoma patients treated with GKRS. **METHODS:** Seventeen institutions pooled clinical data obtained from pituitary adenoma patients who were treated with GKRS from 1988 to 2016. Patients who had undergone prior radiotherapy were excluded. A total of 1023 patients met the study inclusion criteria. The treated lesions included 410 nonfunctioning pituitary adenomas (NFPAs), 262 cases of Cushing's disease (CD), and 251 cases of acromegaly. The median follow-up was 51 months (range 6-246 months). Statistical analysis was performed using a Cox proportional hazards model to evaluate factors associated with the development of new-onset hypopituitarism. **RESULTS:** At last follow-up, 248 patients had developed new pituitary hormone deficiency (86 with NFPA, 66 with CD, and 96 with acromegaly). Among these patients, 150 (60.5%) had single and 98 (39.5%) had multiple hormone deficiencies. New hormonal changes included 82 cortisol (21.6%), 135 thyrotropin (35.6%), 92 gonadotropin (24.3%), 59 growth hormone (15.6%), and 11 vasopressin (2.9%) deficiencies. The actuarial 1-year, 3-year, 5-year, 7-year, and 10-year rates of hypopituitarism were 7.8%, 16.2%, 22.4%, 27.5%, and 31.3%, respectively. The median time to hypopituitarism onset was 39 months. In univariate analyses, an increased rate of new-onset hypopituitarism was significantly associated with a lower isodose line (p = 0.006, HR = 8.695), whole sellar targeting (p = 0.033, HR = 1.452), and treatment of a functional pituitary adenoma as compared with an NFPA (p = 0.008, HR = 1.510). In multivariate analyses, only a lower isodose line was found to be an independent predictor of new-onset hypopituitarism (p = 0.001, HR = 1.38). **CONCLUSIONS:** Hypopituitarism remains the most common unintended effect of GKRS for a pituitary adenoma. Treating the target volume at an isodose line of 50% or greater and avoiding whole-sellar radiosurgery, unless necessary, will likely mitigate the risk of post-GKRS hypopituitarism. Follow-up of these patients is required to detect and treat latent endocrinopathies.

[23] Outcome of partially irradiated recurrent nonfunctioning pituitary macroadenoma by gamma knife radiosurgery.

Journal of neuro-oncology. 2018;139(3):767-775
Shen CC, You WC, Sun MH, Lee SD, Tsou HK, Chen YJ, Sheu ML, Sheehan J, Pan HC
PMID: 29948768 DOI: 10.1007/s11060-018-2925-2
BACKGROUND: Gamma knife treatment outcome of large pituitary tumors which are only partially irradiated secondary to immediate proximity to critical structures such as the optic apparatus have not been rigorously studied. **MATERIALS AND METHODS:** From July 2003 to December 2013, there were 41 cases of recurrent or residual nonfunctioning pituitary macroadenoma partially treated with gamma knife radiosurgery (GKRS) because the adenoma obscured part of the optic apparatus on planning SRS MR imaging. **RESULTS:** The follow up period after GKRS was 92.3 +/- 5.6 months. The percentage of tumor coverage with the full dose was 88.5 +/- 0.7%. Five of 43 (11.6%) patients experienced a transient visional decrease and one patient experienced a permanent visual field defect. During the follow up, two patients underwent transphenoidal surgery and one patient had a craniotomy due to tumor progression. Seven patients (16.2%) developed cortisol and thyroxine deficiencies. In multiple variant analyses, transient visual decline was correlated to the tumor volume (> 3.5 cc), percentage of tumor coverage (< 90%), the distance from the optic apparatus to the pituitary stalk (> 15 mm) and percentage of tumor above the orbital apex (65%). **CONCLUSION:** In the limited case of this cohort, we found that partially treated pituitary nonfunctioning macroadenoma yielded a high tumor control rate. However, visual decline as a result of tumor progression or radiation effect can occur in a minority of patients. The radiosurgical technique warrants further study to better define the long-term risk to benefit profile for its use in complex pituitary macroadenoma obscuring part of the optic apparatus.

LEKSELL GAMMA KNIFE SOCIETY

[24] Early versus late Gamma Knife radiosurgery following transsphenoidal surgery for nonfunctioning pituitary macroadenomas: a multicenter matched-cohort study.

Journal of neurosurgery. 2018;129(3):648-657

Pomeraniec IJ, Kano H, Xu Z, Nguyen B, Siddiqui ZA, Silva D, Sharma M, Radwan H, Cohen JA, Dallapiazza RF, Iorio-Morin C, Wolf A, Jane JA, Grills IS, Mathieu D, Kondziolka D, Lee CC, Wu CC, Cifarelli CP, Chytka T, Barnett GH, Lunsford LD, Sheehan JP

PMID: 29076785 DOI: 10.3171/2017.5.JNS163069

OBJECTIVE: Gamma Knife radiosurgery (GKRS) is frequently used 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 imaging-defined progression of tumor. Given the high incidence of adenoma progression after subtotal resection over time, the present study intended to evaluate the effect of timing of radiosurgery on outcome. **METHODS:** This is a multicenter retrospective review of patients with nonfunctioning pituitary macroadenomas who underwent transsphenoidal surgery followed by GKRS from 1987 to 2015 at 9 institutions affiliated with the International Gamma Knife Research Foundation. Patients were matched by adenoma and radiosurgical parameters and stratified based on the interval between last resection and radiosurgery. Operative results, imaging data, and clinical outcomes were compared across groups following early (</= 6 months after resection) or late (> 6 months after resection) radiosurgery. **RESULTS:** After matching, 222 patients met the authors' study criteria (from an initial collection of 496 patients) and were grouped based on early (n = 111) or late (n = 111) GKRS following transsphenoidal surgery. There was a greater risk of tumor progression after GKRS (p = 0.013) and residual tumor (p = 0.038) in the late radiosurgical group over a median imaging follow-up period of 68.5 months. No significant difference in the occurrence of post-GKRS endocrinopathy was observed (p = 0.68). Thirty percent of patients without endocrinopathy in the early cohort developed new endocrinopathies during the follow-up period versus 27% in the late cohort (p = 0.84). Fourteen percent of the patients in the early group and 25% of the patients in the late group experienced the resolution of endocrine dysfunction after original presentation (p = 0.32). **CONCLUSIONS:** In this study, early GKRS was associated with a lower risk of radiological progression of subtotally resected nonfunctioning pituitary macroadenomas compared with expectant management followed by late radiosurgery. Delaying radiosurgery may increase patient risk for long-term adenoma progression. The timing of radiosurgery does not appear to significantly affect the rate of delayed endocrinopathy.

[25] Upfront Gamma Knife radiosurgery for Cushing's disease and acromegaly: a multicenter, international study.

Journal of neurosurgery. 2018;131(2):532-538

Gupta A, Xu Z, Kano H, Sisterson N, Su YH, Krsek M, Nabeel AM, El-Shehaby A, Karim KA, Martinez-Moreno N, Mathieu D, McShane BJ, Martinez-Alvarez R, Reda WA, Liscak R, Lee CC, Lunsford LD, Sheehan JP

PMID: 30117768 DOI: 10.3171/2018.3.JNS18110

OBJECTIVE: Gamma Knife radiosurgery (GKS) is typically used after failed resection in patients with Cushing's disease (CD) and acromegaly. Little is known about the upfront role of GKS for patients with CD and acromegaly. In this study, the authors examine the outcome of upfront GKS for patients with these functioning adenomas. **METHODS:** An international group of 7 Gamma Knife centers sent pooled data from 46 patients (21 with CD and 25 with acromegaly) undergoing upfront GKS to the coordinating center of the study for analysis. Diagnosis was established on the basis of clinical, endocrine, and radiological studies. All patients were treated on a common radiosurgical platform and longitudinally followed for tumor control, endocrine remission, and hypopituitarism. Patients received a tumor median margin dose of 25 Gy (range 12-40.0 Gy) at a median isodose of 50%. **RESULTS:** The median endocrine follow-up was 69.5 months (range 9-246 months). Endocrine remission was achieved in 51% of the entire cohort, with 28% remission in acromegaly and 81% remission for those with CD at the 5-year interval. Patients with CD achieved remission earlier as compared to those with acromegaly (p = 0.0005). In patients post-GKS, the pituitary adenoma remained stable (39%) or reduced (61%) in size. Hypopituitarism occurred in 9 patients (19.6%), and 1 (2.2%) developed third cranial nerve (CN III) palsy. Eight patients needed further intervention, including repeat GKS in 6 and transsphenoidal surgery in 2. **CONCLUSIONS:** Upfront GKS resulted in good tumor control as well as a low rate of adverse radiation effects in the whole group. Patients with CD achieved a faster and far better remission rate after upfront GKS in comparison to patients with acromegaly. GKS can be considered as an upfront treatment in carefully selected patients with CD who are unwilling or unable to undergo resection, but it has a more limited role in acromegaly.

[26] Technique of Whole-Sellar Stereotactic Radiosurgery for Cushing Disease: Results from a Multicenter, International Cohort Study.

World neurosurgery. 2018;116:e670-e679

Shepard MJ, Mehta GU, Xu Z, Kano H, Sisterson N, Su YH, Krsek M, Nabeel AM, El-Shehaby A, Kareem KA, Martinez-Moreno N, Mathieu D, McShane BJ, Blas K, Kondziolka D, Grills I, Lee JY, Martinez-Alvarez R, Reda WA, Liscak R, Lee CC, Lunsford LD, Lee Vance M, Sheehan JP

PMID: 29783006 DOI: 10.1016/j.wneu.2018.05.067

BACKGROUND: Stereotactic radiosurgery (SRS) is used to manage patients with Cushing disease (CD) who have failed surgical/medical management. Because many patients with recurrent/persistent CD lack an identifiable adenoma on neuroimaging, whole-sellar SRS has been increasingly used. Thus, we sought to define the outcomes of patients undergoing whole-sellar SRS. **METHODS:** An international, multicenter, retrospective cohort design was used to define clinical/endocrine outcomes for patients undergoing whole-sellar SRS for CD. Propensity-score matching was used to compare patients undergoing whole-sellar SRS and patients who underwent discreet adenoma-targeted SRS. **RESULTS:** A total of 68 patients underwent whole-sellar SRS, with a mean endocrine follow-up of 5.3 years. The mean treatment volume was 2.6 cm(3), and the mean margin dose was 22.4 Gy. The 5-year actuarial remission rate was 75.9%, and the median time to remission was 12-months. Treatment volumes >1.6 cm(3) were associated with shorter times to remission (P < 0.05). The 5-year recurrence-free survival rate was 86.0%. Decreased margin and maximum treatment doses were associated with recurrence (P < 0.05). New pituitary hormone deficiency occurred in 15 patients (22.7%). An additional 210 patients were identified who underwent adenoma-targeted SRS. There was no difference in remission rate, time to remission, recurrence-free survival or new endocrinopathy development between patients who underwent whole-sellar SRS and those who underwent discreet adenoma-targeted SRS. **CONCLUSIONS:** Whole-sellar GKRS is effective in controlling CD when an adenoma is not clearly defined on imaging or when an invasive adenoma is suspected at the time of initial surgery. Patients who undergo whole-sellar SRS have outcomes and rates of new pituitary hormone deficiency similar to those of patients who undergo discrete adenoma-targeted GKRS.

[27] Hypopituitarism After Single-Fraction Pituitary Adenoma Radiosurgery: Dosimetric Analysis Based on Patients Treated Using Contemporary Techniques.

International journal of radiation oncology, biology, physics. 2018;101(3):618-623

Graffeo CS, Link MJ, Brown PD, Young WF Jr, Pollock BE

PMID: 29678524 DOI: 10.1016/j.ijrobp.2018.02.169

PURPOSE: To analyze factors associated with post-stereotactic radiosurgery (SRS) hypopituitarism among radiation-naive patients with pituitary adenomas who underwent single-fraction SRS between 2007 and 2014. **METHODS AND MATERIALS:** This was a retrospective review of 97 patients having single-fraction SRS from 2007 until 2014. Eligible patients had no history of prior radiation, normal age- and sex-specific pituitary function before SRS, and at least 24 months of endocrine follow-up. Forty patients (41%) had hormone-secreting tumors; 57 patients had nonsecreting tumors (59%). The median prescription isodose volume was 2.8 cm(3) (interquartile range [IQR], 1.3-4.7); the median tumor margin dose

was 20 Gy (IQR, 15-25 Gy). **RESULTS:** The median follow-up after SRS was 48 months (IQR, 34-68 months). Twenty-seven patients (28%) developed pituitary insufficiency at a median of 22 months (IQR, 12-36 months) after SRS. The rate of new endocrine deficits was 17% at 2 years (95% confidence interval [CI] 10%-25%) and 31% at 5 years (95% CI 20%-42%). Male sex (hazard ratio [HR] 2.38, 95% CI 1.05-5.26, P = .04), smaller pituitary gland volume (HR 0.99, 95% CI 0.99-0.99, P = .01), and higher mean pituitary gland dose (HR 1.31, 95% CI 1.16-1.47, P < .001) were associated with post-SRS hypopituitarism in multivariable analysis. The rate of hypopituitarism for patients with a mean gland dose of <11.0 Gy at 2 years was 2% (95% CI 0%-4%) and at 5 years was 5% (95% CI 0%-11%), whereas rate of hypopituitarism for patients with a mean gland dose of >/=11.0 Gy at 2 years was 31% (95% CI 17%-43%) and at 5 years was 51% (95% CI 34%-65%). **CONCLUSIONS:** Hypopituitarism after pituitary adenoma SRS increases in a time- and dose-dependent manner. Reducing the radiation exposure to the identifiable gland to a mean dose < 11.0 Gy whenever feasible may lower the incidence of new hormonal deficits after pituitary adenoma SRS.

[28] Endocrine Remission After Pituitary Stereotactic Radiosurgery: Differences in Rates of Response for Matched Cohorts of Cushing Disease and Acromegaly Patients.

International journal of radiation oncology, biology, physics. 2018;101(3):610-617
Trifiletti DM, Xu Z, Dutta SW, Quinones-Hinojosa A, Peterson J, Vance ML, Sheehan JP
PMID: 29678528 DOI: 10.1016/j.ijrobp.2018.02.023
PURPOSE: To compare and describe the time to endocrine remission and new hypopituitarism among patients with growth hormone (GH) and adrenocorticotropic hormone (ACTH)-secreting pituitary adenomas after radiosurgery, controlling for several known prognostic factors. **METHODS AND MATERIALS:** An institutional review board-approved, institutional retrospective analysis of patients with GH- and ACTH-secreting pituitary adenomas was performed, with matching for patient sex, age at radiosurgery, interval between the last resection and radiosurgery, use of previous radiation therapy, whole sella treatment, suprasellar extension, cavernous sinus invasion, and margin dose. Endocrine remission was defined as a normal serum insulin-like growth factor-1 (GH secreting) or a normal 24-hour urine-free cortisol (ACTH secreting) level without suppressive medications. Endocrine remission and the incidence of new hypopituitarism after single-fraction radiosurgery were recorded and compared between the 2 groups. **RESULTS:** The data from 242 patients were evaluated, 121 with GH-secreting tumors and 121 with ACTH-secreting tumors. Of the 242 patients, 75% had cavernous sinus invasion and 10% had suprasellar extension at radiosurgery. The median radiosurgical marginal dose was 25 Gy to the 50% isodose line between each group. After multivariable adjustment, the factors associated with an increased time to endocrine remission included patient age (hazard ratio [HR] 1.016; P = .023), cavernous sinus invasion (HR 1.793; P = .004), and the presence of acromegaly (HR 2.912; P < .001). The incidence of new hypopituitarism developing after stereotactic radiosurgery was 29% and did not appreciably differ by adenoma subtype (P = .180). **CONCLUSIONS:** After radiosurgery, patients with ACTH-secreting tumors achieved endocrine remission sooner than did those with GH-secreting tumors. These results provide insight into the relative tumor biology and disease course after radiosurgery that will serve to further improve clinical outcomes and patient treatment in the future.

[29] Long-Term Outcome of Nonfunctioning and Hormonal Active Pituitary Adenoma After Gamma Knife Radiosurgery.

World neurosurgery. 2018;114:e824-e832
Narayan V, Mohammed N, Bir SC, Savardekar AR, Patra DP, Bollam P, Nanda A
PMID: 29574220 DOI: 10.1016/j.wneu.2018.03.094
INTRODUCTION: Stereotactic radiosurgery (SRS), particularly Gamma Knife radiosurgery (GKRS) is an established treatment option for residual and recurrent pituitary adenoma tumors. It helps in the preservation of surrounding normal neuronal, vascular, and hormone-producing structures and causes fewer neurologic deficits. The aim of this research was to evaluate the efficacy and define the role of GKRS in the treatment of nonfunctioning (NFA) and hormonal active (HAA) pituitary adenoma. **METHODS:** A retrospective analysis of 111 patients with histologically proven pituitary adenoma who underwent GKRS treatment at Louisiana State University Health Sciences Center, Shreveport, Louisiana, USA, over a 17-year period was conducted presented. The clinical and radiologic data were collected from the database. The tumors were categorized into NFA and HAA based on the endocrinology profile. The relevant statistical analysis was conducted with SPSS software, version 22.0. **RESULTS:** The median age of the patients was 58 years. The study comprised 87 patients with NFA and 24 patients with HAA tumors. Thirty-eight patients (34.2%) had hypopituitarism symptoms, and 8 patients (7%) had panhypopituitarism symptoms. The mean tumor volume before to GKRS was 3.8 cm(3). Suprasellar and cavernous extension of the tumor was noted in 28 patients (25.2%) and 34 (30.6%) patients, respectively. We observed >70% reduction in the size of tumors in the shrinkage cohort after GKRS; the median time for shrinkage was 48.4 months. However, increase in tumor size was noted in the progression cohort (pre-GKRS 3.8 cm(3) vs. post-GKRS 6.5 cm(3)). Seventy patients (63.1%) had neurologic improvement, and 26 patients (23.4%) had endocrinologic worsening after GKRS. **CONCLUSIONS:** GKRS plays a significant role in the treatment of NFA and HAA. It affords a high rate of tumor control and offers a low risk of collateral neurologic or endocrine axis injury. Our study shows that control of tumor growth was achieved in 90% of patients, shrinkage of tumor in 54%, and arrest of progression in 36% after GKRS treatment. The biochemical remission rate in growth hormone secreting adenoma was 57%, in adrenocorticotropic hormone adenoma 67%, and prolactinoma 40%. Age below 50 years and tumor volume less than 5 cm(3) were associated with a favorable radiosurgical outcome.

[30] Factors affecting early versus late remission in acromegaly following stereotactic radiosurgery.

Journal of neuro-oncology. 2018;138(1):209-216
Patibandla MR, Xu Z, Sheehan JP
PMID: 29417401 DOI: 10.1007/s11060-018-2792-x
Stereotactic radiosurgery (SRS) is a well-established treatment modality for patients with acromegaly. Our previously published study demonstrated a median time to remission of 29 months. This study aims to identify factors affecting the timing of remission and also to quantify the rate of late remission. This is a retrospective analysis of acromegaly patients who underwent SRS between 1988 and 2016. Early and late remissions were defined based on our prior median remission time of 29 months. The median imaging and endocrine follow-ups are 66 and 104.8 months, respectively. Multivariate analysis was conducted to analyze factors leading to late remission. A total number of 157 patients, of those 102 (64.9%) patients achieved remission. of those 102 patients, 62 patients (60.7%) had remission in less than 29 months (early remission) whereas 40 patients (39.3%) achieved remission later than (late remission) 29 months. The two groups differed significantly in the time interval between the last resection and the first SRS (p = 0.040) whole sella radiosurgery (p = 0.025) or radiosurgery to the cavernous sinus (p = 0.041). Competing risk analysis showed the interval between resection and SRS was significantly longer in the late remission group (HR 1.013, 95% CI 1.004-1.02; p = 0.007). Fifty-one of 157 patients (32.5%) developed a new endocrine deficiency following SRS. Those with shorter time between resection and SRS were more likely to achieve early remission. While most patients achieve remission in less than 4 years, the latency of effect with SRS yields a small percentage of patients achieving remission beyond that time point.

[31] Postoperative Gamma Knife Radiosurgery for Cavernous Sinus-Invading Growth Hormone-Secreting Pituitary Adenomas.

World neurosurgery. 2018;110:e534-e545
Kim EH, Oh MC, Chang JH, Moon JH, Ku CR, Chang WS, Lee EJ, Kim SH
PMID: 29155347 DOI: 10.1016/j.wneu.2017.11.043
OBJECTIVE: We aimed to determine the long-term effects of Gamma knife

radiosurgery (GKS) on remnants in the cavernous sinus (CS) after transsphenoidal surgery (TSS) for acromegaly and to identify its possible adverse effects. **METHODS:** Thirty patients who had remnant tumors only inside the CS after TSS and who consequently underwent GKS were included. They were followed for a median period of 47 months after GKS with regular hormonal and radiologic examinations. **RESULTS:** The mean tumor volume and margin dose irradiated by GKS was 3.7 cm(3) and 26.2 Gy, respectively. Radiologic tumor control was identified in all patients, and no tumor regrowth or recurrent tumors were identified. For 14 patients who achieved endocrinologic remission, the median duration from GKS until remission was 35 months. The actuarial rates of remission at 2, 5, and 10 years were 7.1%, 43.6%, and 65.6%, respectively. The degree of decrease in the nadir GH level in the OGTT at 6 months after GKS was a statistically significant predictor of remission. Newly developed hypopituitarism frequently developed in a time-dependent manner. Radiation necrosis developed in 4 patients with relatively large remnant volumes. **CONCLUSIONS:** GKS is an effective adjuvant treatment option for remnant tumors inside the CS after TSS. Maximal surgical resection, leaving minimal volume of remnants only inside the CS, allows the safe and sufficient delivery of a radiation dose to tumors, thereby increasing the possibility of remission. However, the risk of new hypopituitarism and radiation necrosis should be considered when tumors inside the CS are treated with GKS.

2017

[32] Stereotactic Radiosurgery for Cushing Disease: Results of an International, Multicenter Study.

The Journal of clinical endocrinology and metabolism. 2017;102(11):4284-4291
Mehta GU, Ding D, Patibandla MR, Kano H, Sisterson N, Su YH, Krsek M, Nabeel AM, El-Shehaby A, Kareem KA, Martinez-Moreno N, Mathieu D, McShane B, Blas K, Kondziolka D, Grills I, Lee JY, Martinez-Alvarez R, Reda WA, Liscak R, Lee CC, Lunsford LD, Vance ML, Sheehan JP
PMID: 28938462 DOI: 10.1210/jc.2017-01385
Context: Cushing disease (CD) due to adrenocorticotropic hormone-secreting pituitary tumors can be a management challenge. **OBJECTIVE:** To better understand the outcomes of stereotactic radiosurgery (SRS) for CD and define its role in management. Design: International, multicenter, retrospective cohort analysis. Setting: Ten medical centers participating in the International Gamma Knife Research Foundation. Patients: Patients with CD with >6 months endocrine follow-up. Intervention: SRS using Gamma Knife radiosurgery. Main Outcome Measures: The primary outcome was control of hypercortisolism (defined as normalization of free urinary cortisol). Radiologic response and adverse radiation effects (AREs) were recorded. **RESULTS:** In total, 278 patients met inclusion criteria, with a mean follow-up of 5.6 years (0.5 to 20.5 years). Twenty-two patients received SRS as a primary treatment of CD. Mean margin dose was 23.7 Gy. Cumulative initial control of hypercortisolism was 80% at 10 years. Mean time to cortisol normalization was 14.5 months. Recurrences occurred in 18% with initial cortisol normalization. Overall, the rate of durable control of hypercortisolism was 64% at 10 years and 68% among patients who received SRS as a primary treatment. AREs included hypopituitarism (25%) and cranial neuropathy (3%). Visual deficits were related to treatment of tumor within the suprasellar cistern ($P = 0.01$), whereas both visual ($P < 0.0001$) and nonvisual cranial neuropathy ($P = 0.02$) were related to prior pituitary irradiation. **CONCLUSIONS:** SRS for CD is well tolerated and frequently results in control of hypercortisolism. However, recurrences can occur. SRS should be considered for patients with persistent hypercortisolism after pituitary surgery and as a primary treatment in those unfit for surgery. Long-term endocrine follow-up is essential after SRS.

[33] Prognostic significance of corticotroph staining in radiosurgery for non-functioning pituitary adenomas: a multicenter study.

Journal of neuro-oncology. 2017;135(1):67-74
Cohen-Inbar O, Xu Z, Lee CC, Wu CC, Chytka T, Silva D, Sharma M, Radwan H, Grills IS, Nguyen B, Siddiqui Z, Mathieu D, Iorio-Morin C, Wolf A, Cifarelli CP, Cifarelli DT, Lunsford LD, Kondziolka D, Sheehan JP
PMID: 28913674 DOI: 10.1007/s11060-017-2520-y
Silent corticotroph staining pituitary adenoma (SCA) represents an uncommon subset of Non-Functioning adenomas (NFAs), hypothesized to be more locally aggressive. In this retrospective multicenter study, we investigate the safety and effectiveness of Stereotactic Radiosurgery (SRS) in patients with SCA compared with other non-SCA NFA's. Eight centers participating in the International Gamma-Knife Research Foundation (IGKRF) contributed to this study. Outcomes of 50 patients with confirmed SCAs and 307 patients with confirmed non-SCA NFA's treated with SRS were evaluated. Groups were matched. SCA was characterized by a lack of clinical evidence of Cushing disease, yet with positive immunostaining for corticotroph. Median age was 55.2 years (13.7-87). All patients underwent at least one trans-sphenoidal tumor resection prior to SRS. SRS parameters were comparable as well. Median follow-up 40 months (6-163). Overall tumor control rate (TCR) 91.2% (n = 280). In the SCA group, TCR were 82% (n = 41) versus 94.1% (n = 289) for the control-NFA ($p = 0.0065$). The SCA group showed a significantly higher incidence of new post-SRS visual deficit ($p < 0.0001$) assigned to tumor progression and growth, and post-SRS weakness and fatigue ($p < 0.0001$). In univariate and multivariate analysis, only the status of silent corticotroph staining ($p = 0.005$, $p = 0.009$ respectively) and margin dose ($p < 0.0005$, $p = 0.0037$ respectively) significantly influenced progression rate. A margin dose of >/=17 Gy was noted to influence the adenoma progression rate in the entire cohort ($p = 0.003$). Silent corticotroph staining represents an independent factor for adenoma progression and hypopituitarism after SRS. A higher margin dose may convey a greater chance of TCR.

[34] Frequency, pattern, and outcome of recurrences after gamma knife radiosurgery for pituitary adenomas.

Endocrine. 2017;56(3):595-602
Losa M, Spatola G, Albano L, Gandolfi A, Del Vecchio A, Bolognesi A, Mortini P
PMID: 27688011 DOI: 10.1007/s12020-016-1081-8
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.

[35] Treatment of Nonfunctional Pituitary Adenoma Postoperative Remnants: Adjuvant or Delayed Gamma Knife Radiosurgery?

World neurosurgery. 2017;100:361-368

Sadik ZHA, Voormolen EHJ, Depauw PRAM, Burhani B, Nieuwlaat WA, Verheul J, Leenstra S, Fleischeuer R, Hanssens PEJ
PMID: 28108427 DOI: 10.1016/j.wneu.2017.01.028
OBJECTIVE: It is still not clear whether Gamma Knife radiosurgery (GKRS) for nonfunctional pituitary adenomas should be used as a standard adjuvant postoperative therapy or applied when there is documented progression of the remnant on follow-up magnetic resonance imaging. **METHODS:** We performed a retrospective study of patients with nonfunctional pituitary adenomas who underwent primary surgery and GKRS between 2002 and 2015. Patients were divided into 2 groups on the basis of the GKRS indication: adjuvant treatment (GKRS </=6 months postoperatively) or delayed treatment (GKRS if documented progression occurred on the follow-up magnetic resonance imaging). **RESULTS:** Fifty patients were included and grouped based on adjuvant (n = 13) or delayed (n = 37) GKRS following primary surgery. The adjuvant and delayed groups had 10-year actuarial tumor control rates of 92% and 96% (P = 0.408), respectively. The 10-year actuarial endocrinologic control rate was 82% for the adjuvant group and 49% for the delayed group (P = 0.597). None of the patients developed any new neurologic deficit post-GKRS. GKRS-induced complications (intratumoral bleeding and tumoral tissue inflammation) occurred in 6% of the patients, of whom 4% were in the delayed group and 2% in the adjuvant group. **CONCLUSION:** Adjuvant treatment with GKRS yields the same high long-term tumor control as delayed GKRS. Neither adjuvant nor delayed GKRS induced additional neurologic complications. There is a trend that adjuvant GKRS induces less additional endocrinologic deficits compared with delayed GKRS.

2016

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

Journal of neurosurgery. 2016;125(1):202-12
Pomeraniec IJ, Dallapiazza RF, Xu Z, Jane JA Jr, Sheehan JP
PMID: 26517773 DOI: 10.3171/2015.5.JNS15581
OBJECTIVE: 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 subtotally 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.

[37] Primary Endoscopic Transnasal Transsphenoidal Surgery for Giant Pituitary Adenoma.

World neurosurgery. 2016;91:121-8
Kuo CH, Yen YS, Wu JC, Chang PY, Chang HK, Tu TH, Huang WC, Cheng H
PMID: 27060516 DOI: 10.1016/j.wneu.2016.03.092
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 cm(3). 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 cm(3) 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.

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

Clinical neurology and neurosurgery. 2016;145:8-13
Fu P, He YS, Cen YC, Huang Q, Guo KT, Zhao HY, Xiang W
PMID: 27060661 DOI: 10.1016/j.clineuro.2016.03.021
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.

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

Clinical endocrinology. 2016;84(4):524-31
Cohen-Inbar O, Ramesh A, Xu Z, Vance ML, Schlesinger D, Sheehan JP
PMID: 26341248 DOI: 10.1111/cen.12938
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 cm(3) (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.

2015

[40] Gamma Knife radiosurgery for medically and surgically refractory prolactinomas: long-term results.
Pituitary. 2015;18(6):820-30
Cohen-Inbar O, Xu Z, Schlesinger D, Vance ML, Sheehan JP
PMID: 25962347 DOI: 10.1007/s11102-015-0658-1
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.

[41] Clinical and Radiologic Outcome of Gamma Knife Radiosurgery on Nonfunctioning Pituitary Adenomas.
Journal of neurological surgery. Part B, Skull base. 2015;76(5):351-7
Bir SC, Murray RD, Ambekar S, Bollam P, Nanda A
PMID: 26401476 DOI: 10.1055/s-0035-1549309
OBJECTIVE: To elucidate the role of Gamma Knife radiosurgery (GKRS) in the management of nonfunctioning pituitary adenomas (NFAs). **MATERIALS AND METHODS:** A retrospective review of 57 consecutive patients spanning 2000 to 2013 with NFAs was performed. Of 57 patients, 53 patients had recurrent or residual tumors after microsurgical resection. The study population was evaluated clinically and radiographically after GKRS treatment. The median follow-up time was 45.57 months. **RESULTS:** GKRS in pituitary adenomas showed significant variations in tumor growth control (decreased in 32 patients [56.1%], arrested growth in 21 patients [36.1%], and increased tumor size in 4 patients [7%]). Progression-free survival after GKRS at 3, 7, and 10 years was 100%, 98%, and 90%, respectively. The neurologic signs and symptoms were significantly improved after GKRS (14% versus 107%) compared with pretreated signs and symptoms ($p < 0.0001$). Five patients (8.8%) required additional treatment. **CONCLUSION:** Recent follow-up revealed that GKRS offers a high rate of tumor control and preservation of neurologic functions in both new and recurrent patients with NFAs. Thus GKRS is an effective treatment option for recurrent and residual as well as newly diagnosed patients with NFAs.

[42] Stereotactic radiosurgery for acromegaly: outcomes by adenoma subtype.
Pituitary. 2015;18(3):326-34
Lee CC, Vance ML, Lopes MB, Xu Z, Chen CJ, Sheehan J
PMID: 24925503 DOI: 10.1007/s11102-014-0578-5
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.

[43] Long-term results of endonasal endoscopic transsphenoidal resection of nonfunctioning pituitary macroadenomas.
Neurosurgery. 2015;76(1):42-52; discussion 52-3
Dallapiazza RF, Grober Y, Starke RM, Laws ER Jr, Jane JA Jr
PMID: 25255271 DOI: 10.1227/NEU.0000000000000563
BACKGROUND: Several studies report early results of endoscopic endonasal transsphenoidal surgery; however, none discuss long-term outcome measures such as tumor recurrence rates and the need for additional surgical procedures. **OBJECTIVE:** To discuss the long-term outcomes after endoscopic endonasal transsphenoidal surgery for nonfunctioning pituitary macroadenomas.

METHODS: This is a retrospective study. Patients were included only if they had at least 5 years of clinical and imaging follow-up after surgery. **RESULTS:** Eighty patients met the study criteria. Grossly complete resection was achieved in 71% of patients. Knosp grade 0 to 2 tumors and tumor with volumes <10 cm were significantly more likely to have received a grossly complete resection. There were 7 recurrences (12%) in patients who had received grossly complete resections, with a mean time to recurrence of 53 months. Among the 23 patients who had subtotal resections, 11 (61%) progressed radiographically, and 3 (17%) had symptomatic progression. Knosp score, surgical and radiographic evidence of invasion, and preoperative visual deficits were predictive of recurrence in a univariate analysis, but Knosp grade was the only independent predictor in a multivariate analysis. Kaplan-Meier analysis projected a 10-year progression-free survival rate of 80% and 21% for patients with gross total resections and subtotal resections, respectively. **CONCLUSION:** At the long-term follow-up, 12% of patients had recurrent tumors after grossly complete resection. Recurrent or residual tumors were treated with either repeat surgery or Gamma Knife radiosurgery. Rates of complete resection, postoperative surgical and endocrinological complications, and additional surgical procedures are similar to previously published reports after microscopic transsphenoidal surgery.

2014

[44] Clinical experiences and success rates of acromegaly treatment: the single center results of 62 patients.

BMC endocrine disorders. 2014;14:97
Evran M, Sert M, Tetiker T
PMID: 25511633 DOI: 10.1186/1472-6823-14-97
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. **RESULTS:** 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. 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.

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

International journal of radiation oncology, biology, physics. 2014;90(4):903-10
Xu Z, Ellis S, Lee CC, Starke RM, Schlesinger D, Lee Vance M, Lopes MB, Sheehan J
PMID: 25216855 DOI: 10.1016/j.ijrobp.2014.07.013
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-adrenocorticotropic 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.

[46] Dose-volume analysis of radiation-induced optic neuropathy after single-fraction stereotactic radiosurgery.

Neurosurgery. 2014;75(4):456-60; discussion 460
Pollock BE, Link MJ, Leavitt JA, Stafford SL
PMID: 24902082 DOI: 10.1227/NEU.0000000000000457
BACKGROUND: The risk of radiation-induced optic neuropathy (RION) is the primary limitation of single-fraction stereotactic radiosurgery (SRS) for many patients with parasellar lesions. **OBJECTIVE:** To define the normal tissue complication probability of the anterior visual pathways (AVPs) 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 (interquartile range [IQR], 6.9-10.8). One hundred seventy-four sides (65%) received >8 Gy: the median 8-Gy volume was 15.8 mm(3) (IQR, 3.7-36.2). Ninety-four sides (35%) received >10 Gy; the median 10-Gy volume was 1.6 mm(3) (IQR, 0.5-5.3). Twenty-nine sides (11%) received >12 Gy; the median 12-Gy volume was 0.1 mm(3) (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% confidence interval) in this series were 0% to 2.6%, 0% to 4.7%, and 0% to 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 normal tissue complication probability 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 parasellar region.

LEKSELL GAMMA KNIFE SOCIETY

[47] Whole-sellar stereotactic radiosurgery for functioning pituitary adenomas.
Neurosurgery. 2014;75(3):227-37; discussion 237
Lee CC, Chen CJ, Yen CP, Xu Z, Schlesinger D, Fezeu F, Sheehan JP
PMID: 24867204 DOI: 10.1227/NEU.0000000000000425
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.

[48] Efficacy and safety of higher dose stereotactic radiosurgery for functional pituitary adenomas: a preliminary report.
World neurosurgery. 2014;82(1-2):195-201
Grant RA, Whicker M, Lleva R, Knisely JP, Inzucchi SE, Chiang VL
PMID: 23385448 DOI: 10.1016/j.wneu.2013.01.127
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.

[49] Stereotactic radiosurgery for acromegaly.
The Journal of clinical endocrinology and metabolism. 2014;99(4):1273-81
Lee CC, Vance ML, Xu Z, Yen CP, Schlesinger D, Dodson B, Sheehan J
PMID: 24471574 DOI: 10.1210/jc.2013-3743
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.

[50] Repeated transsphenoidal surgery or gamma knife radiosurgery in recurrent cushing disease after transsphenoidal surgery.
Journal of neurological surgery. Part A, Central European neurosurgery. 2014;75(2):91-7
Bodaghabadi M, Riazi H, Aran S, Bitaraf MA, Alikhani M, Alahverdi M, Mohamadi M, Shalileh K, Azar M
PMID: 23965751 DOI: 10.1055/s-0033-1345688
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.

[51] Initial Gamma Knife radiosurgery for nonfunctioning pituitary adenomas.
Journal of neurosurgery. 2014;120(3):647-54
Lee CC, Kano H, Yang HC, Xu Z, Yen CP, Chung WY, Pan DH, Lunsford LD, Sheehan JP
PMID: 24405068 DOI: 10.3171/2013.11.JNS131757
OBJECTIVE: 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.

[52] Cushing's disease: a single centre's experience using the linear accelerator (LINAC) for stereotactic radiosurgery and fractionated stereotactic radiotherapy.
Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia. 2014;21(1):100-6
Wilson PJ, Williams JR, Smee RI
PMID: 24074805 DOI: 10.1016/j.jocn.2013.04.007
Cushing's disease is hypercortisolaemia secondary to an adrenocorticotrophic hormone secreting pituitary adenoma. Primary management is almost always surgical, with limited effective medical interventions available. Adjuvant therapy in the form of radiation is gaining popularity, with the bulk of the literature related to the Gamma Knife. We present the results from our own institution using the linear accelerator (LINAC) since 1990. Thirty-six patients who underwent stereotactic radiosurgery (SRS), one patient who underwent fractionated stereotactic radiotherapy (FSRT) and for the purposes of comparison, 13 patients who had undergone conventional radiotherapy prior to 1990, were included in the analysis. Serum cortisol levels improved in nine of 36 (25%) SRS patients and 24 hour urinary free cortisol levels improved in 13 of 36 patients (36.1%). Tumour volume control was excellent in the SRS group with deterioration in only one patient (3%). The patient who underwent FSRT had a highly aggressive tumour refractory to radiation.

2013

[53] Results of gamma knife surgery for Cushing's disease.
Journal of neurosurgery. 2013;119(6):1486-92
Sheehan JP, Xu Z, Salvetti DJ, Schmitt PJ, Vance ML
PMID: 23930850 DOI: 10.3171/2013.7.JNS13217
OBJECTIVE: 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.

[54] Gamma Knife radiosurgery for the management of nonfunctioning pituitary adenomas: a multicenter study.
Journal of neurosurgery. 2013;119(2):446-56
Sheehan JP, 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
PMID: 23621595 DOI: 10.3171/2013.3.JNS12766
OBJECTIVE: 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.

LEKSELL GAMMA KNIFE SOCIETY

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

The Canadian journal of neurological sciences. Le journal canadien des sciences neurologiques. 2013;40(4):546-52

Zeiler FA, Bigder M, Kaufmann A, McDonald PJ, Fewer D, Butler J, Schroeder G, West M

PMID: 23786738 DOI: 10.1017/s0317167100014645

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%) adrenocorticotropic 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 5.41cm(3), 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.

[56] Hypopituitarism after stereotactic radiosurgery for pituitary adenomas.

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

Xu Z, Lee Vance M, Schlesinger D, Sheehan JP

PMID: 23277375 DOI: 10.1227/NEU.0b013e3182846e44

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 adrenocorticotropic 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.

2012

[57] Gamma knife radiosurgery for clinically persistent acromegaly.

Journal of neuro-oncology. 2012;109(1):71-9

Liu X, Kano H, Kondziolka D, Park KJ, Iyer A, Niranjan A, Flickinger JC, Lunsford LD

PMID: 22535434 DOI: 10.1007/s11060-012-0862-z

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.

[58] Dosimetric factors associated with pituitary function after Gamma Knife Surgery (GKS) of pituitary adenomas.

Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2012;104(1):119-24

Sicignano G, Losa M, del Vecchio A, Cattaneo GM, Picozzi P, Bolognesi A, Mortini P, Calandrino R

PMID: 22647658 DOI: 10.1016/j.radonc.2012.03.021

BACKGROUND AND PURPOSE: Gamma Knife Surgery (GKS) can be an adjunctive option to surgery in the case of pituitary adenomas. The effect of dosimetric variables on the incidence of new anterior pituitary deficits after GKS requires better definition. **MATERIALS AND METHODS:** This retrospective study considered 130 patients with a follow up after GKS >6 months. The diagnosis was nonfunctioning pituitary adenoma (NFPA) in 68 patients and secreting pituitary adenoma (SPA) in 62 patients. Median margin dose was 15/25 Gy for NFPA and SPA, respectively. The endocrinological median follow-up was 60 months. Hypopituitarism was defined as a new pituitary deficit in (at least) one of the three hormonal axes (hypogonadism, hypothyroidism and hypoadrenalism). The predictive value of clinical/dosimetric parameters was tested by univariate/multivariate analyses. **RESULTS:** Sixteen patients (12.3%) showed a new pituitary deficit in one or more axes. Multivariate analysis confirmed that the mean dose to the stalk/pituitary and the amount of healthy tissue within the high dose region were strong independent predictors of pituitary dysfunction; their best cut-off values were around 15.7 Gy, 7.3 Gy and 1.4 cm(3), respectively. **CONCLUSIONS:** Our data showed a dose-dependent incidence of new hormonal deficits after GKS for pituitary adenoma. During planning definition, the risk of hypopituitarism could be reduced using the outlined safe dose-volume values.

LEKSELL GAMMA KNIFE SOCIETY

[59] Gamma Knife surgery for patients with nonfunctioning pituitary macroadenomas: predictors of tumor control, neurological deficits, and hypopituitarism.

Journal of neurosurgery. 2012;117(1):129-35
Starke RM, Williams BJ, Jane JA Jr, Sheehan JP
PMID: 22577749 DOI: 10.3171/2012.4.JNS112250

OBJECTIVE: Nonfunctioning pituitary macroadenomas often recur after microsurgery and thereby require further treatment. Gamma Knife surgery (GKS) has been used to treat recurrent adenomas. In this study, the authors evaluated outcomes following GKS of nonfunctioning pituitary macroadenomas and assessed predictors of tumor control, neurological deficits, and delayed hypopituitarism. **METHODS:** Between June 1989 and March 2010, 140 consecutive patients with nonfunctioning pituitary macroadenomas were treated using GKS at the University of Virginia. The median patient age was 51 years (range 21-82 years), and 56% of patients were male. Mean tumor volume was 5.6 cm3 (range 0.6-35 cm3). Thirteen patients were treated with GKS as primary therapy, and 127 had undergone at least 1 open resection prior to GKS. Ninety-three patients had a history of hormone therapy prior to GKS. The mean maximal dose of GKS was 38.6 Gy (range 10-70 Gy), the mean marginal dose was 18 Gy (range 5-25 Gy), and the mean number of isocenters was 9.8 (range 1-26). Follow-up evaluations were performed in all 140 patients, ranging from 0.5 to 17 years (mean 5 years, median 4.2 years). **RESULTS:** Tumor volume remained stable or decreased in 113 (90%) of 125 patients with available follow-up imaging. Kaplan-Meier analysis demonstrated radiographic progression free survival at 2, 5, 8, and 10 years to be 98%, 97%, 91%, and 87%, respectively. In multivariate analysis, a tumor volume greater than 5 cm3 (hazard ratio=5.0, 95% CI 1.5-17.2; p=0.023) was the only factor predictive of tumor growth. The median time to tumor progression was 14.5 years. Delayed hypopituitarism occurred in 30.3% of patients. No factor was predictive of post-GKS hypopituitarism. A new or worsening cranial nerve deficit occurred in 16 (13.7%) of 117 patients. Visual decline was the most common neurological deficit (12.8%), and all patients experiencing visual decline had evidence of tumor progression. In multivariate analysis, a tumor volume greater than 5 cm3 (OR=3.7, 95% CI 1.2-11.7; p=0.025) and pre-GKS hypopituitarism (OR=7.5, 95% CI 1.1-60.8; p=0.05) were predictive of a new or worsened neurological deficit. **CONCLUSIONS:** In patients with nonfunctioning pituitary macroadenomas, GKS confers a high rate of tumor control and a low rate of neurological deficits. The most common complication following GKS is delayed hypopituitarism, and this occurs in a minority of patients.

[60] Results of gamma knife radiosurgery in acromegaly.

International journal of endocrinology. 2012;2012:342034
Franzin A, Spatola G, Losa M, Picozzi P, Mortini P
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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.

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

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OBJECTIVE: 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.