

CLINICAL STUDY

Gamma knife stereotactic radiosurgery for acromegaly

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Abstract

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

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

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

Setting: Norwegian National Center for gamma knife treatment.

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

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

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

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Introduction

In cases of acromegaly where surgery is contraindicated or does not lead to cure, either conventional fractionated radiotherapy (CRT) or single dose gamma knife radiosurgery (GKR) may be used as adjuvant or primary therapies. Although the technique of CRT has been improved (1), it takes many years to obtain normalization of hypersecretion. Adverse effects, in particular pituitary failure, are common (2–4).

GKR is assumed to reduce hypersecretion more rapidly than CRT, whilst keeping the adverse effects at a low level (5, 6), but the number of patients reported is altogether low and the definition criteria for endocrine cure and hypopituitarism vary greatly between studies, making comparison difficult (7–18). The elapsed time from when

GKR treatment is given until full effect is obtained is several years, and in many series the follow-up time is short. Some target parameters, such as the kinetics of growth hormone (GH) and insulin-like growth factor I (IGF-I) secretion, as well as the need for GH-suppressive medication post-GKR, are poorly characterized.

To evaluate the therapeutic and adverse effects of GKR of patients with acromegaly, we conducted a cross-sectional study of 53 out of 61 acromegaly patients treated at one gamma knife (GK) center from January 1989 until June 2002. The patients were submitted to a predefined, multidisciplinary survey taking into account the recent criteria for cure (19). In addition, based on all post-GKR GH and IGF-I values from each patient, we calculated kinetics for decline of hormone hypersecretion following GKR.

Subjects and methods

Study population

The GK unit in Norway is located at Haukeland University Hospital, Bergen, and patients are recruited from the 4.6 million Norwegian population. From January 1989 to December 2002, 127 patients were treated for tumors in the pituitary region; 61 of these were acromegaly patients who had not received any other radiation to the sella (Table 1). All patients had clinical signs of acromegaly together with radiologically visualized pituitary tumor, and elevated IGF-I and GH or dependence on somatostatin analogs for control of GH hypersecretion. In eight patients (six died, two were unable to attend survey control), retrospective data were used for evaluation. The causes of death were lymphoma (non-CNS), cerebral aneurysm rupture, cardiac failure, and acute abdominal illness, and in two patients the cause of death was unknown.

Treatment

Radiosurgery was performed with a 201-source Co⁶⁰ Leksell model C GK (Elekta Instruments, Stockholm, Sweden). After stereotactic frame placement, the tumor coordinates were defined using contrast-enhanced CT or magnetic resonance imaging (MRI). MRI has been used routinely from 1996. The KULA dose planning system was replaced by the GammaPlan system in 1996 (both Elekta Instruments), and the automatic positioning system was introduced at the same time. Since 1998, we have withdrawn somatostatin analogs at least 8 weeks before GKR. All patients were followed post-GKR by routine endocrinology at 6–12 months intervals until survey.

The dose plan aimed at delivering at least 25 Gy to the tumor periphery at the 50% isodose. This was

Table 1 Population characteristics and treatment data for 61 patients receiving gamma knife radiosurgery for acromegaly at the Department of Neurosurgery, Haukeland University Hospital (1989–2002). For continuous numbers, mean (range) are given.

N (male)	61 (32)
Age, mean (years)	47 (18–81)
Dead	6
Elevated prolactin levels	4
Follow-up, years	5.5 (1.1–14.7)
Follow-up > 5 years	31
Tumor volume (cm ³)	1.23 (0.010–6.60)
GH at GKR (mIU/l)	28.1 (0.60–442)
IGF-I at GKR (nmol/l)	69.2 (18.5–184)
Previous transphenoidal surgery (more than one procedure)	56 (12)
Time from surgery to GKR (years)	3.7 (0.24–17)
GKR within 1 year after surgery	22
Treatment isodose (%)	49.5 (30–70)
Treatment maximal dose (Gy)	53.4 (24–70)
Dose to periphery (Gy)	26.5 (12–35)
Tumor coverage dose (%)	89.7 (54–100)
Dose to chiasm (Gy)	6.8 (0.3–16.2)

achieved in 43 patients. In 10 patients, the isodose was below 50%, and in 15 patients, the dose to tumor periphery was below 25 Gy. The optic pathways received <10 Gy, except in nine cases receiving from 10 and up to 12 Gy, and in three receiving 12, 13, and 16 Gy (Table 1). This dose was given to a very limited volume of the nerve and was done because the shape and volume of a portion of tumor had close apposition to the optic apparatus.

Collection of data

Retrospective data and statistical analysis Treatment dose plans, radiological images, hormone substitutions, GH-suppressive medication, eye status, and hormone values were collected from the patients' medical journals. All patients were routinely followed by endocrinologist in the interval between GKR and survey.

To analyze the dynamics of GH and IGF-I secretion, we collected all IGF-I and GH values obtained from GKR through to survey or last follow-up for the 55 patients who were alive. Patients were grouped depending on whether or not they had received hormone-suppressive medication, and the two groups of patients were analyzed separately. Data were compiled and time series generated for each patient. One outlying low value for IGF-I and one for GH were, after careful consideration, classified as unreasonable and removed from further analysis. The kinetics of reductions in GH and IGF-I levels were analyzed by nonlinear mixed effects models for IGF-I and GH values by time since GKR using the R package nlme (20). Fixed model parameters were the value at GKR, a horizontal asymptote and an exponential rate of decline for the deviation from the asymptote. All parameters were entered on a log scale to enhance model stability and ensure positive values. Interindividual random effects were originally included in all three parameters, with simplification of the random structure and graphical model diagnostics as recommended by Pinheiro & Bates (20). The intraindividual errors were added to log-transformed values of the response to reduce possible heteroscedasticity. Nonlinear generalized least squares models were fitted in case of serious problems with the mixed effects model. Halftimes for the deviation from the asymptotic value were calculated from the models' fixed effects estimates.

For all other statistical analysis, SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) and R (The R Foundation for Statistical Computing, Vienna, Austria) were used. Data were analyzed using Student's *t*-tests, Kaplan–Meier statistics, χ^2 tests, and univariate Cox regression analysis.

Cross-sectional data During the 2 days, the patients underwent a study protocol including MRI, hormone evaluation, and clinical examination by a neurosurgeon, an endocrinologist, and an ophthalmologist. Of the 53

patients who underwent the full study protocol, 48 attended this at Haukeland University Hospital, whereas 5 underwent a similar survey in other centers. The study adhered to the tenets of the Declaration of Helsinki, and the protocol was approved without review by the Regional Medical Research Ethics Committee.

Radiological examination: T1 contrast-enhanced MRI scans were used for evaluation of changes in tumor size. Survey MRI scans were examined for signs of temporal lobe necrosis and radiation injuries. All eligible MRI scans from the GKR procedure (34 in GammaPlan, 13 in hardcopies) were compared with MRI scans performed at survey. Due to technical limitations caused by old MRI technology, and small tumor volumes in many cases (<1.2 ml tumor volume in 42 cases), more than 50% volume change was considered significant.

Endocrinological examination: A clinical evaluation of symptoms indicating hormone hypersecretion and pituitary dysfunction was performed. Laboratory analysis included morning urine- and serum osmolality and morning serum hormone levels. Reference values at Haukeland University Hospital: IGF-I; 19–30 years, 15–63 nmol/l; 31–55 years, 11–40 nmol/l; > 55 years, 7–29 nmol/l; adrenocorticotropin (ACTH) 2.0–11.6 pmol/l; cortisol 138–690 nmol/l, thyrotropin (TSH) 0.3–3.6 mIU/l; free thyroxine (T4) 7.6–19.7 pmol/l; follicle-stimulating hormone (FSH) 0.7–11.1, IE/l (21.7–153 IE/l in menopausal women); luteinizing hormone (LH) 0.8–7.6 IE/l; estradiol females 14–50 years, 80–2100 pmol/l; > 50 years, 6–100 pmol/l; testosterone males 9.5–40.0 nmol/l; and prolactin 53–360 mIU/l. The quantification of GH and IGF-I was done in a routine laboratory using the Immulite 2000 hGH and IGF-I solid-phase chemiluminescent immunometric assays (Euro/DPC, Gwynedd, UK). For GH, the conversion factor is $2.6 \times \text{ng/ml}$ for conversion into mIU/l (WHO NIBSC 1st IS 80/505). For IGF-I, the conversion factor is $0.13 \times \text{ng/ml}$ into nmol/l (WHO NIBSC 1st IRR 87/518).

Twenty patients with normal age-adjusted IGF-I levels and GH levels above 2.6 mIU/l were submitted to an oral glucose GH-suppression test (OGT), which was done at 8 weeks after withdrawal of GH suppression therapy, if any. Patients were given 75 g glucose, and the OGT was considered normal if the GH nadir was 2.6 mIU/l or less. If nadir GH and age-adjusted IGF-I were both normal after 8 weeks, patients were followed for at least 1 year after survey before a conclusion regarding a full cure was determined.

An insulin-tolerance test (ITT) was performed in 35 cases. In 19 patients not eligible to undertake ITT (unwilling $n=2$, steroid medication $n=9$, heart disease or epilepsy $n=8$), the corticotrophic axis was evaluated using baseline morning cortisol and ACTH levels, serum electrolyte levels and by medical history. An adequate stimulus (serum glucose below 2.2 mmol/l and/or symptoms of hypoglycemia) was obtained in all patients tested except one. The GH response was considered

normal if the peak GH level was above 9 mIU/l. The corticotrophic axis response was considered adequate if the peak serum cortisol level was above 550 nmol/l or increased with more than 200 nmol/l.

Gonadotrophic deficiency was defined by low plasma testosterone and non-elevated FSH/LH levels in men, low plasma estradiol with low FSH/LH in premenopausal women and lack of elevated FSH/LH in menopausal women. Thyretropic deficiency was defined as a low-T4 with normal or low TSH levels. ADH deficiency was defined by urine osmolality below 300 mosmol/kg, raised serum osmolality above 310 mosmol/kg, and clinical diabetes insipidus.

Ophthalmological examination: Routine ophthalmological examination was performed that included visual acuity testing (Snellen charts), slit lamp examination, funduscopy, motility testing, and Ishihara's test for color vision. Testing for visual field defects was performed using automated perimetry (Octopus 101 (Haag Streit, Switzerland), program 07). The visual field charts were compared with those obtained before GKR.

Results

Information about GKR treatment (Table 1) and hormone replacement therapy post-GKR was retrospectively collected for all 61 patients. The kinetics of GH and IGF-I are based on retrospectively collected IGF-I and GH values from the 55 living patients. Data on results of treatment (cure, radiology, and other adverse effects) are presented for the 53 patients who underwent the full survey protocol.

Radiological examination

In 22 patients, tumor shrinkage was 50% or more. In 25 patients, no significant change in tumor volume was found. In the remaining six, the treatment was based on CT or scans were missing and a comparison was not possible. No cases of tumor growth, temporal lobe necrosis, or other adverse effects were found.

Endocrine hypersecretion

Retrospective data From GKR to 10 years follow-up, there was a continuous rise in the proportion of patients displaying normal IGF-I and GH levels below 5 mIU/l. At 5 years, 58% had normal baseline IGF-I and 51% of patients had normal baseline GH levels (Fig. 1). Only one patient received additional non-pharmacological adjuvant therapy and was operated 3.8 years after GKR.

The levels of IGF-I and GH (393 and 422 samples respectively from 55 patients) declined toward lower levels following GKR, and then stabilized (Fig. 2). In the subgroup of 42 patients receiving hormone-suppressive drugs at any time, the mean IGF-I level at GKR

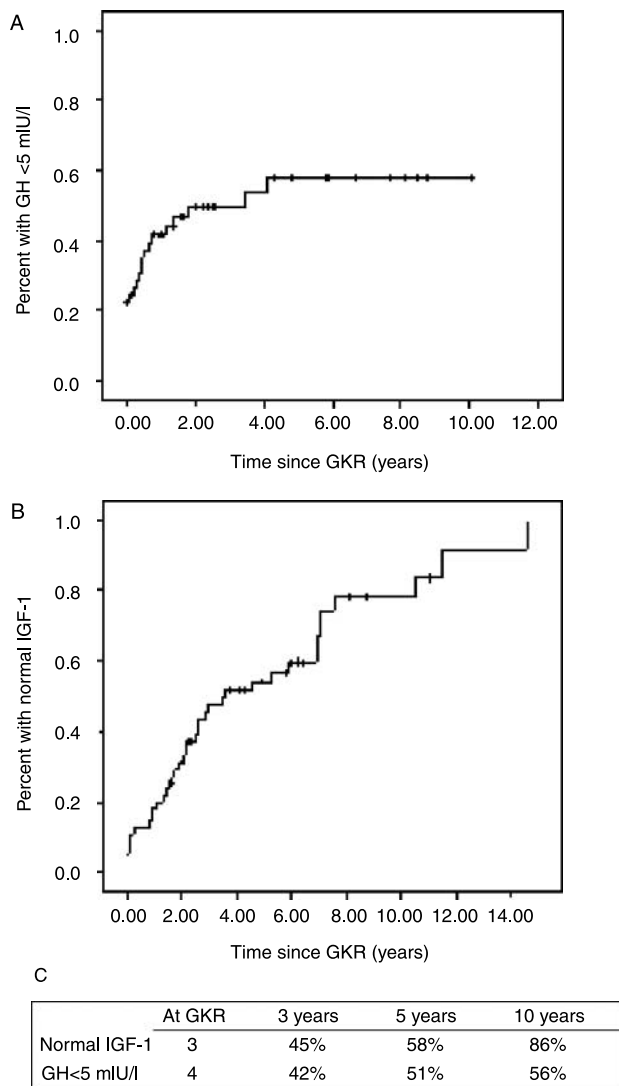


Figure 1 Cumulative normalization in acromegaly patients treated by GKR during the years 1989–2002. (A) GH values. (B) IGF values. (C) Proportion of patients with normal IGF-I and baseline GH < 5 mIU/l at GKR, and at 3, 5, and 10 years follow-up based on Kaplan–Meier statistics of retrospective data.

treatment was 55 nmol/l (95% confidence interval; range 45–68), the asymptotic value was 29 nmol/l (24–34), and the halftime toward this level was 1.1 years (0.80–1.5). For GH, the corresponding estimates were 11.8 mIU/l (7.7–18) (GH at GKR), 4.4 mIU/l (3.7–5.3) (asymptote), and 0.54 years (0.23–1.3) (halftime).

In the 13 patients who did not receive GH-suppressive drugs at any time, the values were 48 nmol/l (43–54) (IGF-I at GKR), 3.2 nmol/l (0.28–37) (asymptote), and 7.4 years (3.5–15) (halftime). For GH, the corresponding estimates were 7.9 mIU/l (5.5–11) (GH at GKR), 1.2 mIU/l (0.083–18) (asymptotic value), and 4.1 years (1.0–16) (halftime).

The IGF-I drop was more rapid in patients who received suppressive therapy than in those who never

received any such treatment (non-overlapping confidence intervals). Otherwise the differences between groups were not significant. Hormone decline in six patients who received octreotide during GKR was not significantly different from the remaining, but some of these patients stopped taking the drug after GKR.

Survey data Of the 53 patients who underwent a full survey protocol, 45 patients had a reduction of IGF-I levels, when compared with the levels at GKR. Mean GH was reduced from 20 ± 25 mIU/l at GKR to 7.9 ± 7.1 mIU/l ($P < 0.0005$) and mean IGF-I from 71 ± 38 to 33 ± 16 nmol/l ($P < 0.0005$). Normal or low age-adjusted IGF-I and baseline GH levels < 5 mIU/l were found in 20 (38%) of cases, in which 9 were on GH-suppressive medication (Table 2).

Altogether, 40 out of the 53 survey patients had received GH-suppressive medication, 29 patients were still on suppressive medication at survey, and 20 of these had normal IGF-I levels. Four patients could not be taken off GH-suppressive medication (two had just started medication and two were unwilling). Out of 20, 16 of the group agreed to drug withdrawal, and at retesting 8 weeks off drug, 7 had normal IGF-I, and 5 had GH below 2.6 mIU/l at OGT. These five remained free from relapse for at least 1 year of further follow-up. Thus after survey, 24 out of 53 patients received GH-suppressive medication.

In total, nine patients had normal age-adjusted IGF-I and GH nadir < 2.6 mIU/l at OGT without suppressive medication (19) (Table 2). This is 17% of the patients who underwent the full survey protocol. Three patients had low IGF-I levels comparable with GH deficiency. Hormone levels at GKR were not significantly different between cured (GH 14 ± 6.7 mIU/l, IGF-I 70 ± 45 nmol/l) and non-cured patients (GH 31 ± 70 mIU/l, IGF-I 71 ± 37 nmol/l; $P = 0.47$ and 0.91, accordingly). Tumor size, tumor coverage, dose to periphery, maximum dose, or number of isocenters were not significantly associated with cure ($P = 0.61$ –0.98).

Adverse effects

Cranial nerves Normal pre- and postoperative perimetry examinations were obtained in 40 patients. Seven additional cases not examined before GKR also had normal visual fields. New minor, asymptomatic peripheral visual field defects (VFD) were found in two patients who had received chiasm doses of 8.4 and 10.9 Gy. In four patients where VFD was diagnosed prior to GKR, repeated perimetry was normal in two at survey. Reduced visual acuity found in seven patients was ascribed to cataract, diabetic retinopathy, and other eye disease. No patients reported diplopia or trigeminal symptoms.

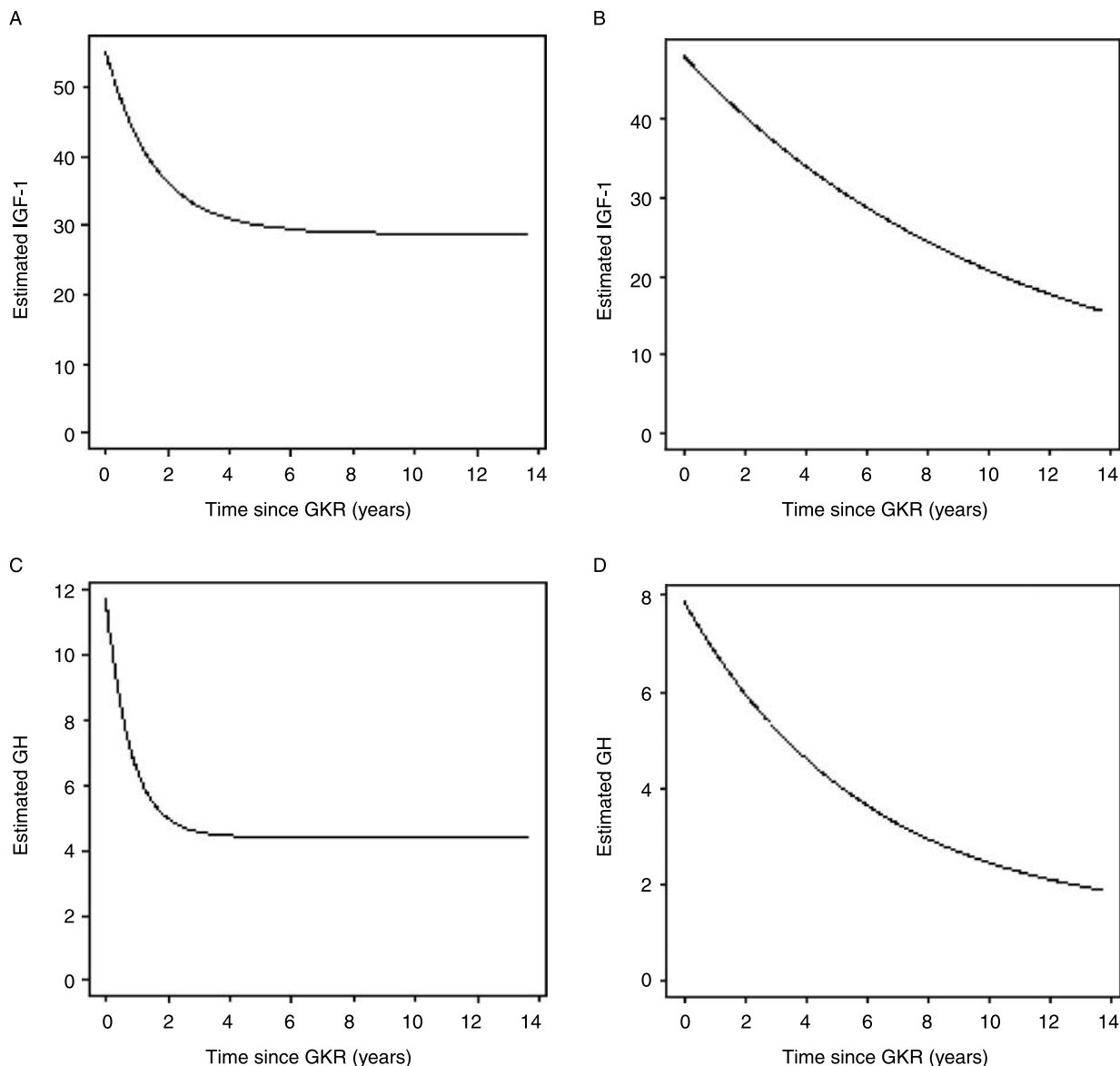


Figure 2 Kinetics of IGF-I (A and B) and GH (C and D) following GKR in 40 patients with acromegaly receiving GH-suppressive medication post-GKR (A and C) and in 13 non-medicated patients (B and D). Model-based estimates.

Pituitary failure Based on journal records for all 61 patients, as well as survey data, 14 new pituitary hormone axes needed substitution therapies (Table 3), whereas 5 patients each had a withdrawal of hormone substitution in one axis post-GKR. In four patients, substitution was started in one axis, two patients needed two substitutions, and another two needed three new substitutions. Thus, 8 out of 61 patients (13%) required new hormone substitution after GKR treatment. The actuarial survival rate free from any new substitution therapy was 94% at 5 years and 82% at 10 years (Fig. 3). We did not find any association between post-GKR hormone substitution and any of the following: maximum dose, dose to periphery, number of

isocenters (univariate Cox regression, $P=0.65-0.91$), pre-GKR pituitary failure, previous surgery, or complete cure (Kaplan–Meier analysis with log-rank test, $P=0.21-0.85$).

Table 2 Effect of gamma knife radiosurgery on growth hormone (GH) hypersecretion in 53 patients who underwent full survey.

	Fraction	Patients
Reduction of hypersecretion	0.85	45
Normal IGF-I and GH below 13 mIU/l	0.57	30
Normal IGF-I and GH below 5 mIU/l	0.38	20
Normal IGF-I and OGT-GH nadir <2.6 mIU/l, without GH-suppressive medication	0.17	9

Table 3 New hormone substitution therapy in 57 out of 61 gamma knife radiosurgery-treated patients with acromegaly 1989–2002. In four patients, data were missing.

	At treatment	At last follow-up
Free from any substitution	40 (70%)	38 (67%)
One substitution	12 (21%)	11 (19%)
Two substitutions	5 (8.8%)	4 (7.0%)
Three substitutions	0	4 (7.0%)

At survey, 3 patients out of 53 had low GH and IGF-I levels, thus having developed GH deficiency (Table 4). None of these patients received GH substitution. The fraction of patients developing such a deficiency was thus 0.057.

Ten patients received corticosteroid-substitution therapy when given GKR. After GKR, corticosteroid substitution was withdrawn in four and started in five patients. Four additional patients had previously unrecognized defects in the corticotrophic axis detected by ITT at survey. The fraction of patients developing a hypofunctioning corticotrophic axis was 0.18, while the fraction of corticosteroid substitution therapy that was stopped was 0.40.

Prior to GKR, two patients had been operated for primary hyperthyreosis with thyroid gland resection. Another eight patients had thyroxin substitution at the time of GKR treatment not related to other causes, and three had started thyroxin substitution during the follow-up period. Thus, the fraction of normal functioning axes at GKR developing the need for thyroxin substitution was 0.059. No new failures of the thyretropic axis were found at survey.

The mean patient age was 47 years at treatment and 53 years at survey. In the interval, four men were given testosterone and two women estrogen, while

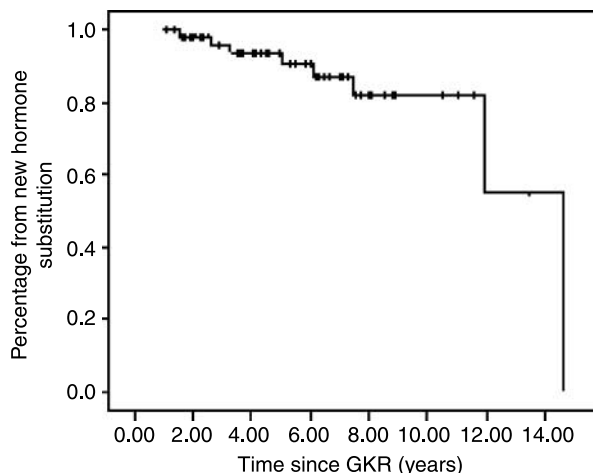


Figure 3 Actuarial survival free from new hormone substitutions in 61 patients receiving GKR for acromegaly 1989–2002.

Table 4 Treatment of failing pituitary axes before gamma knife radiosurgery (GKR) and during clinical follow-up in 57 out of 61 GKR-treated patients with acromegaly 1989–2002. In four patients, data were missing.

Treated axes	Cortico-tropic	Thyreo-tropic	Gonado-tropic	Somato-tropic
Substituted at GKR	10	8	4	NA
Substituted at survey	11	11	9	0
Additional defects discovered by ITT	4			3

testosterone was withdrawn in one male patient. In 38 patients who were aged below 55 years at survey, the number of patients requiring sex hormone substitution increased from four to nine after GKR. Thus, in this group, the fraction of substitution in the sex hormone axis was 0.15. No new sex hormone deficiencies were detected at survey. No patients developed AVP (ADH) deficiency.

Cerebrovascular morbidity One patient with known heart disease developed memory loss and unilateral hemiparesis a few hours after GKR. The symptoms reversed, but minor sequelae were permanent. No ischemic injury was detectable by CT at the time of treatment or at follow-up MRI.

Discussion

Disease control

This study confirms others (17, 21) in showing tumor growth arrest following GKR for acromegaly. Additional surgery is rarely required (16). In both aspects, the results resemble those reported for CRT (22, 23).

GH and IGF-I levels in acromegaly both correlate with mortality and morbidity, but if the nadir GH level is kept below 1 µg/l and age-adjusted IGF-I is normal, this is indicative of a normal life expectancy (24). A possible health benefit is acquired even if the strictest criteria for full cure (19) are not obtained. We found a reduction in hypersecretion in 85% of cases, although it must be noted that pre-GKR GH and IGF-I levels in some of our patients were normal due to ongoing somatostatin analog treatment. There has been substantial variation in the definition criteria for cure of acromegaly. To report in accordance with recent consensus guidelines (19), we used OGT in our survey and found that only 17% of patients suppressed GH below the upper limit, and three patients had signs of GH deficiency. At GKR, very few patients had undergone an OGT. Similarly, we did not perform a suppression test in patients who were on drugs at survey. Therefore, we cannot report the number of patients with controlled disease on drug at treatment and survey.

The evaluation of GKR effect on hormone levels has varied greatly among publications, and comparisons are therefore difficult. We reviewed 10 studies encompassing altogether 302 GKR-treated acromegaly patients, where criteria for cure were both normalization of IGF-I and a stated cut-off level for GH (7, 10, 12–18, 35; Table 5). The cut-off GH values varied between 2 and 7 µg/l, and cure rates between 20 and 100%. A weighted analysis showed a normalization rate of 47% at 45 months, which is quite similar to the 57% with normal age-adjusted IGF-I and GH below 13 mIU/l found in the present study (Table 2).

We could not confirm, as some reports on CRT and GKR treatments for acromegaly (7, 23) have suggested, that a good effect of GKR is dependent on low pretreatment GH and IGF-I levels. Although the cured patients had a mean GH level at GKR that was only half that of non-cured patients, a significant level of difference was not reached. This may be due to the fact that the numbers of patients are few and the variation in hormone levels between patients is large. It is possible that the use of somatostatin analogs may also confound this finding.

We found that IGF-I and GH levels became reduced and then stabilized above zero. Although normalization was achieved in many cases, there was considerable variation in the long-term limiting value for GH as well as for IGF-I. The regression model performed poorer for GH than for IGF-I, because the diurnal secretion of GH leads to more widespread data. Landolt *et al.* (12) reported that within 1.4 years after GKR, hypersecretion became reduced to a level similar to that obtained 7.1 years after CRT. A decline rate similar to the latter has been described in several reports on CRT for acromegaly (3, 4, 23), and GH/IGF-I levels apparently continue to decline towards nil. For GKR, a rate similar to Landolt's and the one presented in this study is reported by Castinetti *et al.* (7) who, similar to our data, showed that an initial phase of rapid decline was followed by stabilization. In contrast, the medically naïve patients reported here responded to GKR in a slower but more prolonged drop phase. This is similar to the data presented by Jezkova *et al.* (18) who found GH values declining to levels below 5 mIU/l during 5 years following GKR. In the group of 13 patients who never received any GH-suppressive medication, the isolated effect of GKR on hypersecretion is demonstrated. Our data indicate that patients who received hormone suppression responded more rapidly to GKR than those who did not. Only six patients received octreotide while they got GKR. We did not observe any radioprotective effect caused by octreotide (25) within this small group.

The analysis of kinetics was based on routine clinical hormone values collected and analyzed at two centers over a 12-year period from 1989 to 2002. Changes in assay systems during this time may provide a source of error, in particular since the commercial kits used for such analyses are subject to some variation. In a

Table 5 Data from 10 studies using defined GH and IGF-I levels to describe effect of GKR treatment, comprising altogether 302 patients with acromegaly. For comparison, GH and IGF-I levels have been converted into SI units (see Subjects and methods).

Criteria	No. patients	Cure rate (%)	Tumor volume (cm ³)	Dose to periphery (Gy)	Maximum dose (Gy)	Follow-up (months)	GH at GKR (ng/ml)	IGF-I at GKR (ng/ml)
Attanasio <i>et al.</i> (36)	30	23	1.4	20	NR	46	10	624
Castinetti <i>et al.</i> (7)	82	43	NR ^a	26	NR	49.5	22	653
Fukuoka <i>et al.</i> (10)	9	50	4.9	19	41	42	71	NR
Landolt <i>et al.</i> (12)	16	81	NR ^b	25	50	17	7	89.2 mIU/l ^c
Jezkova <i>et al.</i> (18)	96	57	1.4	32	63	54	20	944
Mokry <i>et al.</i> (13)	16	31	2.9	16	33	46	21	900 IU/ml ^{c,d}
Morange-Ramos <i>et al.</i> (14)	15	20	1.5	28	NR	20	38	612
Petrovich <i>et al.</i> (15)	6	100	5.3 ^e	15 ^e	30 ^e	41	21	895
Pollock <i>et al.</i> (16)	26	42	4.3 ^e	20 ^e	40 ^e	42	8.3	305
Shin <i>et al.</i> (17)	6	67	1.1	33	NR	42.7	8.5	781.8
All above	302	47	2.2	26	53	45	20	728
Present study	53	57	1.2	26	53	67.2	10.9	542

^a74 macroadenomas.

^bTumor volume not reported, but the volume listed is derived from a mean diameter of 15.5 mm.

^cNo conversion factor reported.

^dIGF-I value extracted from graph.NR, not reported.

^eData include some patients with other forms of pituitary adenomas.

prospective study with a fixed protocol, such data may be more accurate.

The estimated annual costs of somatostatin analogs per patient (2004) are €10 280 (26). In our study, the drug was withdrawn in 16 patients; a cost reduction of more than €100 000 per year. Drug withdrawal and repeated testing should be considered if GH/IGF-I values become normal.

Adverse effects

In total, adverse effects were few. Previous reports show that 1–3% of pituitary patients develop VFD following GKR (27), in particular if the radiation dose level to the visual pathway is high (28). Although the chiasm dose was higher than 10 Gy in 12 patients, only one asymptomatic, minor VFD were found among these. This is in contrast to the report by Leber *et al.* where VFDs were found in 26.7% of patients receiving 10–15 Gy (28). Other authors, however, report results similar to ours (16, 29). We suggest that this discrepancy may be dependent on the volume of the optic pathway receiving a high dosage of radiation. In the cases reported here, only a minimal volume of the optic pathway received dosages of more than 10 Gy.

In patients with pituitary adenoma, pituitary failure may develop during the course of the disease or after surgery or irradiation. Repeated transsphenoidal surgery carries a reported risk of new pituitary axis hormone failures in between 3.6 and 62.5% of cases (30–32). Patients examined 50 months after CRT require substitutions in 20–50% of previously intact axes (2–4), whereas lower figures (14–23%) are reported after GKR (33, 34 and present study). Although the onset of new hormone substitution therapies is a feasible way of measuring pituitary failure, the timing and need for such substitutions are dependent on the clinical setting, and failing axes may be overlooked. We found a higher number of dysfunctional axes evaluating baseline hormone values and peak values during ITT, than by scoring hormone deficiencies alone. Similarly, Feigl *et al.* (9) found that the number of patients who had low baseline hormone levels was higher than the number receiving hormone substitution therapies in GKR-treated patients. After a follow-up of 4.6 years, 40% developed a declining pituitary function and need for hormone axis substitutions, with a mean latent interval of 11 months. Failing axes were found in 11% (ACTH) to 35% (TSH) of cases, whereas fewer patients (8% (ACTH) to 20% (TSH)) needed substitution therapies. The mean tumor volume (3.8 cm³) and margin doses (50.7 Gy) exceed those of other studies.

In the study by Losa *et al.* (35), 54 patients were followed for 41 months and monitored for pituitary failure. In total, 12.5, 8.6, and 2.3% of gonadotropic, thyrotropic, and corticotropic axes showed failing baseline hormone levels. Attanasio *et al.* (36) found that 2 out of 30 patients followed for 46 months

developed anterior pituitary dysfunction. In the latter two studies, the tumor volumes and margin doses were in the same range as ours. Castinetti *et al.* (7) using ITT to identify corticotrophic deficiency found that 14 of 82 GKR-treated acromegaly patients developed one or more new pituitary deficiencies within 49.5 months.

Three of our patients developed GH deficiency. As the cure criteria for acromegaly have become stricter, the space between cure on one side and GH deficiency (37, 38) on the other has become narrow. Although subgroup analysis of the data presented by Holdaway *et al.* (39) show that the presence of hypopituitarism in acromegaly patients does not have any significant influence on survival, increased mortality has been associated with hypopituitarism in general (40). At the same time, there are no studies that explore whether the strict consensus criteria further differentiate the risk of morbidity and mortality compared with simpler criteria using random GH levels and IGF-I (41). To ensure optimal patient quality of life, further studies should explore the consequences of the strict criteria for definition for acromegalic cure.

Conclusion

Tumor growth arrest was obtained in all patients. As a rule, the reduction of hormone hypersecretion was substantial, rapid, and resulted in stabilization at low levels. According to the strictest definitions 17% of patients with residual disease after surgery became cured. Adverse effects were few. One in seven patients developed a need for new hormone substitution therapies.

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