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Gamma-Knife Radiosurgery in Acromegaly: A 4-Year Follow-Up Study

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Stereotactic radiosurgery by gamma-knife (GK) is an attractive therapeutic option after failure of microsurgical removal in patients with pituitary adenoma. In these tumors or remnants of them, it aims to obtain the arrest of cell proliferation and hormone hypersecretion using a single precise high dose of ionizing radiation, sparing surrounding structures. The long-term efficacy and toxicity of GK in acromegaly are only partially known. Thirty acromegalic patients (14 women and 16 men) entered a prospective study of GK treatment. Most were surgical failures, whereas in 3 GK was the primary treatment. Imaging of the adenoma and target coordinates identification were obtained by high resolution magnetic resonance imaging. All patients were treated with multiple isocenters (mean, 8; range, 3–11). The 50% isodose was used in 27 patients (90%). The mean margin dose was 20 Gy (range, 15–35), and the dose to the visual pathways was always less than 8 Gy. After a median follow-up of 46 months (range, 9–96), IGF-I fell from 805 μg/liter (median; interquartile range, 640–994) to 460 μg/liter (interquartile range, 217–654; $P = 0.0002$), and normal age-matched IGF-I levels were reached in 7 patients (23%). Mean GH levels decreased from 10 μg/liter (interquartile range, 6.4–15) to 2.9 μg/liter (interquartile range, 2–5.3; $P < 0.0001$), reaching levels below 2.5 μg/liter in 11 (37%). The rate of persistently pathological hormonal levels was still 70% at 5 yr by Kaplan-Meier analysis. The median volume was 1.43 ml (range, 0.20–3.7). Tumor shrinkage (at least 25% of basal volume) occurred after 24 months (range, 12–36) in 11 of 19 patients (58% of assessable patients). The rate of shrinkage was 79% at 4 yr. In no case was further growth observed. Only 1 patient complained of side-effects (severe headache and nausea immediately after the procedure, with full recovery in a few days with steroid therapy). Anterior pituitary failures were observed in 2 patients, who already had partial hypopituitarism, after 2 and 6 yr, respectively. No patient developed visual deficits. GK is a valid adjunctive tool in the management of acromegaly that controls GH/IGF-I hypersecretion and tumor growth, with shrinkage of adenoma and no recurrence of the disease in the considered observation period and with low acute and chronic toxicity. (*J Clin Endocrinol Metab* 88: 3105–3112, 2003)

RADIATION AS A treatment modality in pituitary adenomas is as old as surgical removal itself, being attempted in the first years of the past century (1). Currently it includes, besides fractionated conventional radiotherapy (RT), radiosurgery by gamma-knife (GK) and by specially modified linear accelerators and particle accelerators.

In the last 30 yr transsphenoidal surgery has emerged as the initial treatment of choice for acromegaly, because it affords relative safety and the fast reduction of both hormone hypersecretion and tumoral mass. A variety of reasons, including technical difficulty, caution near sensitive structures, and tumor invasion of perisellar structures, hamper successful radical resection in at least 30% of operated patients. Medication, when effective and tolerated, has the drawbacks of a life-long and high cost treatment.

RT has been regarded for a long time as the conventional method for adjuvant therapy. Rates of tumor growth control have been reported to vary from 72–97% (2, 3), whereas control of hormonal hypersecretion is less consistent among different series, ranging from less than 5% of IGF-I normalization (4) to 79% (5). The major drawbacks of RT include the long delay before the desired effect (often a decade) and serious side-effects, including a relatively high rate of hypopituitarism (13–100%) (6–8), potential cerebral necrosis (0–3%) (5, 9), neurobehavioral sequelae (10), low but still significant risks of optic neuropathy (1–2%) (3, 11, 12), and induction of secondary tumor (13, 14).

Radiosurgery, defined as highly precise circumscribed delivery of radiation to a target in a single session (15), performed by either GK or other stereotactic modalities, has been gaining acceptance in recent years to overcome the limitations of RT. The goal is to collimate selectively to the adenoma a high dose of radiation capable of influencing the growth of the tumor and hypersecretion, with negligible irradiation of surrounding normal tissue.

The control of adenoma growth alone that would be enough in other tumoral indications is inadequate in the secreting pituitary adenomas. Radiosurgery of acromegaly to prove a valid therapeutic adjunct ought to correct deranged GH secretion and reverse morbidity and excess mortality by reducing GH below a threshold regarded as safe on

Abbreviations: GK, Gamma-knife; IFMA, immunofluorometric assay; RT, radiotherapy; SA, somatostatin analog; UFC, urinary free cortisol.

the basis of epidemiological studies (16, 17) and decreasing IGF-I to age-adjusted concentrations.

Patients and Methods

Patients

Thirty acromegalic patients (14 women and 16 men) entered this prospective open study from February 1993 to January 2001. All had active disease according to the clinical picture, elevated GH levels not suppressible below 1 μg/liter after an oral glucose load and high age-adjusted IGF-I levels. Three patients (no. 14, 22, and 29) had elevated serum PRL levels. Clinical data are shown in Table 1. Median age at GK was 46 yr (range, 23–68 yr). Three patients (no. 12, 16, and 19), unsuitable for surgery, underwent GK after medical treatment with somatostatin analogs (SA). In one patient (no. 16) this treatment obtained shrinkage of the adenoma away from the optical chiasm, allowing the following treatment by GK. In 27 patients GK was performed 1–18 yr (median, 3 yr) after unsuccessful pituitary surgery (by transfrontal route in two, no. 4 and 11) and was followed by medical therapy. Four of these patients (no. 2, 5, 7, and 10) had also undergone RT. These patients, all irradiated at least 10 yr before GK, showed stable and persistently elevated GH concentrations.

Twelve patients underwent GK while on treatment with long-acting SA (no. 5, 9, 10, 15, 17, 19–21, 23, 25, 27, and 29) and 18 off-treatment.

Before GK, seven patients had TSH deficiency (no. 3, 4, 5, 7, 8, 10, and 13), four had ACTH deficiency (no. 3, 4, 10, and 13), four male patients (no. 2, 3, 4, and 10) had gonadotropin deficiency, seven females were of menopausal age, and none of the premenopausal women had amenorrhea. Posterior pituitary function was normal in all patients.

Methodology of GK treatment

Twenty-seven procedures were performed in a GK model B at one institution (San Raffaele Hospital, Milan, Italy); the remaining three (no. 22, 23, and 27) were performed at three sites in other countries, with similar doses and technique.

A Leksell model G stereotactic frame was applied in all patients under local anesthesia. Imaging was performed within the Leksell frame by high resolution magnetic resonance imaging in all patients, to define the pituitary adenoma volume and settle target coordinates. In selected cases a computed tomography scan was used to overcome geometrical uncertainties.

In a single patient (treated in 1993 in another institution) dose planning was performed using graphical software (KULA, AB Elekta, Stockholm, Sweden) on a Micro-Vax II computer workstation (Digital Equipment Corp., Westminster, MA); in all others treatment planning was performed by dedicated three-dimensional simulation software (Leksell γ Plan AB Elekta).

The neurosurgeon and the radiation physicist decided jointly the treatment isodose, the central dose, and the dose to the margin, with the foremost consideration being given to the radiation dose received by optic chiasm, that was always lower than 8 Gy. The median irradiated volume was 1.43 ml (range, 0.2–3.7). All patients were treated with multiple isocenters (mean, 8; range, 3–11). The 50% isodose was used in 27 patients (90%). The median margin dose was 20 Gy (range, 15–35). Patients were discharged from the hospital on the day after treatment.

Each patient gave informed consent after full explanation of the purpose of the study, which was approved by each local ethic committee, and the procedures followed were in accordance with the Helsinki Declaration of 1975 as revised in 1983.

Protocol

Patients were followed-up at regular intervals, every 3–6 months during the first year and every 6–12 months thereafter. At every visit a careful clinical and ophtalmological evaluation was performed. Ongoing GH-suppressive treatment was periodically withdrawn (at least for

TABLE 1. Demographic and clinical data

Patient no.	Sex	Age[a] (yr)	Previous treatments[b]	Basal GH (μg/liter)	Basal IGF-I (μg/liter)[c]	Follow-up (months)
1	M	45	TS (1996/1997) SA	8.0	600	27
2	M	42	TS (1979), RT (1985), SA	35.0	1400	57
3	M	56	TS (1997), SA	5.3	541	13
4	M	25	TC (1995), SA	10	800	60
5	F	50	TS (1986), RT (1986), SA	15.0	375	55
6	F	43	TS (1988), SA	10.0	1100	56
7	F	44	TS (1984), RT (1984), SA	10.0	700	41
8	M	52	TS (1991/1997), SA	14.0	832	24
9	M	27	TS (1994), SA	11	592	24
10	M	58	TS (1986), RT (1987), DA	6.3	697	45
11	M	46	TC (1991), SA	8.0	850	47
12	F	60	SA	3.0	1000	65
13	F	64	TS (1998), SA	20.0	800	24
14	F	46	TS (1993), SA	82.4	994	60
15	F	68	TS (1985), SA	6.4	1216	60
16	M	49	SA	30	910	60
17	F	46	TS (1992), SA	5.5	727	60
18	F	44	TS (1994), SA	2.9	441	48
19	M	36	SA	11	805	48
20	M	39	TS (1998), SA	13.7	648	18
21	F	67	TS (1978), SA	11.7	1622	36
22	M	67	TS (1996), SA	9.5	589	36
23	M	62	TS (1980), SA	11	864	96
24	F	23	TS (1999), SA	16.8	912	12
25	M	51	TS (1993), SA	6.5	665	48
26	F	37	TS (1995), SA	2.7	857	60
27	F	26	TS (1997), SA	25.5	640	36
28	M	38	TS (1996), SA	4.8	460	18
29	F	59	TS (1996), SA	19.6	673	42
30	M	42	TS (1999), SA	7.6	1423	9

[a] Age at treatment.

[b] Previous treatments (year in *parentheses*): TS, transsphenoidal neurosurgery; TC, transcranic neurosurgery; RT, fractionated conventional radiotherapy; SA, somatostatin analogs; DA, dopamine agonists.

[c] To convert serum IGF-I values to nanomoles per liter, divide by 7.741.

3 months) to evaluate the effects of GK. In a few patients with poor control of disease activity, medical therapy was not withdrawn.

Hormonal data at each control were recorded in two categories, according to whether medical treatment for acromegaly was still ongoing or had been withdrawn. In *Results*, data obtained at each follow-up evaluation are detailed only for patients off medical treatment.

Blood samples were collected in the morning hourly for at least 3 h after an overnight fast and rest while the patients were supine and awake, with an indwelling needle inserted in an antecubital vein and kept patent by slow infusion of saline. GH concentrations were assayed on each sample (in *Results* the reported value is the mean of all samples), and IGF-I levels were determined in the first sample.

In the patients with previously normal pituitary function, assessments of urinary free cortisol (UFC), serum free thyroid hormones, and testosterone (in males) were performed every 3–12 months. The diagnosis of pituitary failure was established on the basis of assays of peripheral hormones showing values below the normal range. Gonadal failure in females was considered only if menstrual cycles terminated before 45 yr with low gonadotropin levels.

GH deficiency was diagnosed when IGF-I levels were lower than the fifth percentile of age-matched range.

Methods

Serum GH levels were measured by an immunofluorometric assay (IFMA) method supplied by AutoDelfia purchased from Wallac, Inc. (Turku, Finland) with standards calibrated against WHO First International Standard 80/505 (1 μg/liter = 2.6 mU/liter). The sensitivity is 0.01 μg/liter; the intra- and interassay coefficients of variation are 2% and 1.7%, respectively.

Serum IGF-I was measured by a RIA supplied by Mediagnost (Tubingen, Germany) with minor modifications. The calibration of this RIA with regard to the WHO International Standard, NIBSC 87/518, yields a conversion factor of 1.66. This kit is able to measure total IGF-I by separating IGF-I from IGF-binding protein by acidification in IGF-II excess. IGF-II cross-reactivity is less than 0.05%; the intra- and interassay coefficients of variation are 3.2% and 7.4% respectively. In our laboratory current normal values for IGF-I (5th-95th percentiles) are 115–338 μg/liter in patients 20–30 yr old, 108–323 μg/liter in patients 30–40 yr old, 100–307 μg/liter in patients 40–50 yr old, 97–294 μg/liter in patients 50–60 yr old, and 91–284 μg/liter in patients 60–70 yr old. To convert serum IGF-I values to nanomoles per liter, divide by 7.741.

PRL was measured by IFMA, and patients were considered hyperprolactinemic when mean circulating serum PRL levels were higher than 25 μg/liter. Also, free T_4, testosterone, and UFC were assayed by commercial IFMA methods, UFC after extraction.

Ophtalmological evaluation was performed by Goldmann or computerized perimetry.

Magnetic resonance imaging was performed by Philips Gyroscan (ACS-NT, Philips Electronic Instruments, Mahway, NJ; 1.5 Tesla) before GK, 6 and 12 months after GK, and yearly thereafter. The annual examination was always performed under the same conditions as far as ongoing treatment or its withdrawal. All scans were reviewed by an author (M.F.), who was unaware of the clinical and biochemical conditions of the patient. On each scan the largest diameter of the tumor was measured on coronal [vertical diameter (V)] and axial sections [anteroposterior (AP) and transverse (T)], calculating the approximate volume of the adenoma as the volume of a rotating ellipsoid, with the following formula (18): volume = π (V $\times$ AP $\times$ T)/6. The shrinkage of the tumor was arbitrarily considered significant when such a volume was reduced by at least 25%.

The follow-up of tumoral modifications after GK was performed only in a subgroup of 19 patients, because little remnant volume due to previous surgery and RT treatments impaired this evaluation in the other 11 patients.

Statistical analysis

Values are expressed as the median and interquartile range (25–75%) unless otherwise stated. Analyses were performed using GB-Stat 6.5.4 PPC on raw data or after transformation of hormonal data as a percentage of the baseline.

Data were analyzed by parametric or nonparametric tests, depending on whether they passed preliminary Kolgomorov-Smirnov test for normality, respectively. Continuous data with normal distribution were analyzed by *t* test for paired or unpaired data, ANOVA followed by Student-Newman-Keuls test, and Pearson correlation test. Continuous data with uneven distribution were analyzed by Wilcoxon test, Mann-Whitney test, Kruskal-Wallis test followed by Dunn test, and Spearman correlation test. Categorical data were analyzed by Fisher's exact test. Longitudinal evaluations were performed by Kaplan-Meier method, and differences between subgroups were evaluated by log-rank test.

All statistical tests were two-tailed, and $P < 0.05$ was considered significant.

Results

Patients were followed-up for a median period of 46 months (range, 9–96). No patient was lost to follow-up.

Hormonal profile

Five patients (no. 4, 9, 10, 20, and 24) at their last evaluation were receiving treatment with SA and/or dopamine agonists due to poor control of the disease despite treatment (on group).

In the remaining 25 patients, evaluated after withdrawal of antisecretory treatment (off group), IGF-I values fell from 805 (range, 640–994) to 460 (range, 217–654) μg/liter (P = 0.0002). Normal age-matched IGF-I levels were obtained in 7 patients (23% of the whole series; Fig. 1A), 24 (range, 13–30) months after GK.

GH levels decreased from 10 (range, 6.4–15) to 2.9 (range, 2–5.3) μg/liter ($P < 0.0001$), reaching levels below 2.5 μg/liter in 11 (37% of the whole series; Fig. 1B) irradiated 24 (range, 18–28) months before.

Both safe GH and normalized IGF-I levels were achieved during prolonged off therapy by seven patients (23%). Moreover, in five patients, who maintained high hormonal levels during medical treatment before GK, the same treatment succeeded in normalizing GH and IGF-I concentrations after GK. A longer follow-up is needed to know exactly the final endocrinological outcome of these patients. Neither basal hormonal levels, volume of the adenoma, length of follow-up, nor dose of radiation were different between patients who achieved and those who did not achieve hormonal normalization.

Hormonal levels before treatment, dose of radiation, and length of follow-up were not different between patients in the off group and those in the on group.

The longitudinal evaluation showed that 1 yr after GK, GH and IGF-I concentrations were 62% (range, 39–79%) and 61% (range, 51–101%) of basal levels, respectively. The respective figures were 49% (range, 28–76%) and 57% (range, 34–73%) after 3 yr, and 25% (16–64%) and 41% (28–47%) after 5 yr (Fig. 2). By Kaplan-Meier analysis, the rate of pathological GH/IGF-I levels fell from 93% at 1 yr to 76% at 3 yr to 70% at 5 yr (Fig. 3).

The outcome of the 4 patients previously submitted to RT was not different from that of the whole series, that of the patients not previously submitted to neurosurgery, or that of the hyperprolactinemic patients. No difference in outcome was observed between patients who had withdrawn SA during irradiation and those still receiving treatment while undergoing GK. In particular, 7 of 18 patients of the former group attained safe GH levels compared with 4 of 12 of the latter (P = 0.53, by Fisher's test; P = 0.85, by log-rank). The

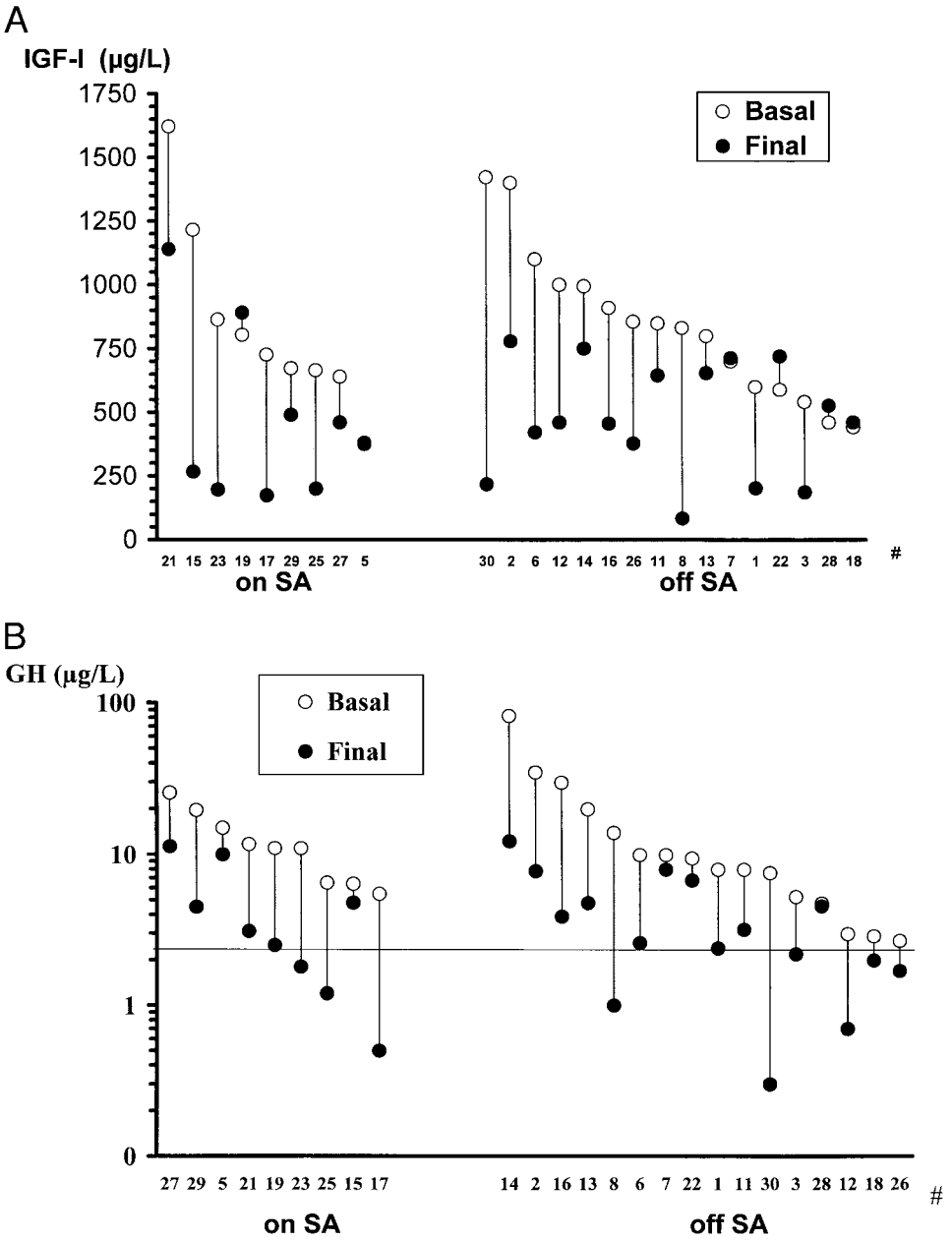

FIG. 1. Individual IGF-I (A) and GH (B; log scale; the horizontal line is set at 2.5 μg/liter) levels before (*empty symbols*) and after (*full symbols*) GK (at the final evaluation). In each panel patients who were submitted to GK while on or off SA are depicted on the *left* and the *right*, respectively. To convert serum IGF-I values to nanomoles per liter, divide by 7.741.

respective figures for IGF-I normalization were 4 and 3. Neither basal hormonal levels before GK nor length of follow-up were different between the 2 subgroups. Sex and age did not influence the outcome of treatment in our range of age groups. No patient had recurrence or worsening of disease.

Tumor size

In no patient was progression of tumor growth observed during follow-up. The median volume of the adenoma decreased to 0.3 (range, 0.1–0.4) ml ($P = 0.001$). Tumor size reduction greater than 25% of basal volume occurred in 11 (no. 2, 4, 6, 11, 12, 16–18, 22, 29, and 30) of the 19 assessable patients (58%) 24 (range, 12–36) months after GK. Individual tumor shrinkage ranged between 6–77% of the basal volume (median, 18%). There was a direct correlation between basal and final volume ($\rho = 0.5975$; $P = 0.0113$), but no relationship between tumor shrinkage and hormonal changes. The rate of tumor shrinkage increased from 28% at 1 yr to 79% at 4 yr, by Kaplan-Meier test (Fig. 3).

Adverse effects

Acute toxicity. One patient (no. 6) developed severe headache and nausea immediately after GK, which recovered within 1 wk with steroid treatment.

Chronic effects. No visual deficit was reported in any patient. Visual fields, repeated in all patients at the last follow-up visit, were unchanged. Prospective assessment of cognitive functions was not performed, but neither the patients nor their relatives reported development of memory impairment

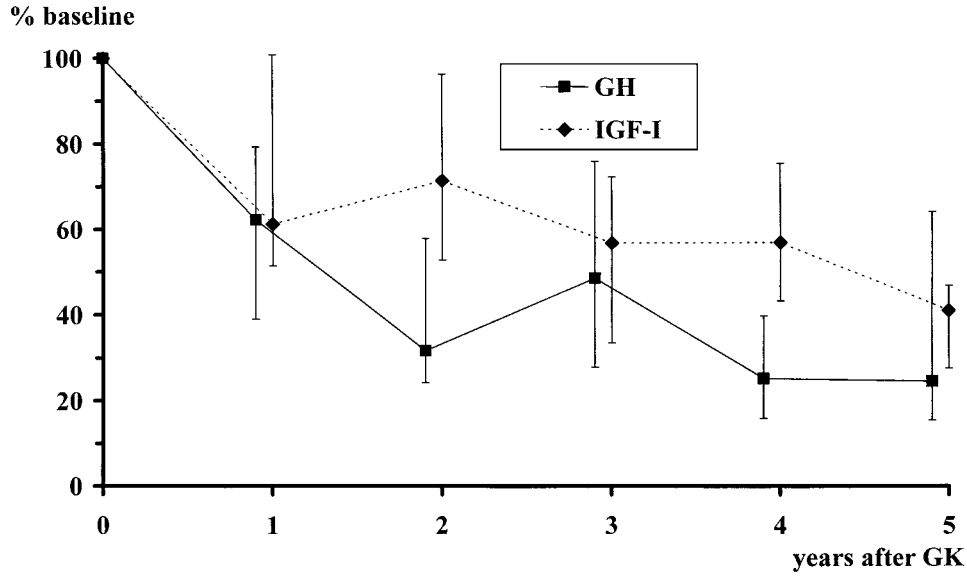

FIG. 2. Percent decrease (median and interquartile) of GH (*squares* and *continuous line*) and IGF-I (*diamonds* and *broken line*) after GK (baseline normalized to 100%).

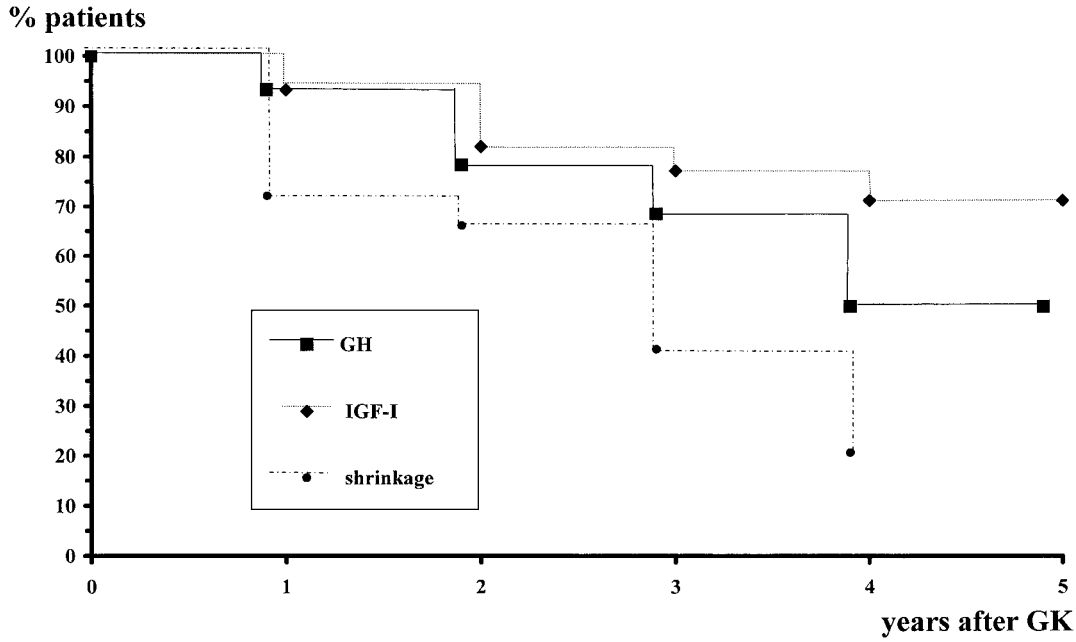

FIG. 3. Kaplan-Meier analysis: achievement of GH safe levels is depicted by *squares* and *continuous line*, IGF-I normalization by *diamonds* and *dotted line*, tumor shrinkage by *circles* and *dotted-broken line*.

on formal inquiry. New anterior pituitary failure was observed in two patients. In patient 12 hypoadrenalism developed 6 yr after GK, when acromegaly was still active. In patient 8 hypogonadism and hypoadrenalism developed 2 yr after GK, concomitantly with normalization of GH and IGF-I hypersecretion, adding to preexisting hypothyroidism. In the other patients no new deficiency was observed beyond minor changes (Fig. 4). No patient developed GH deficiency.

Discussion

The relative role of alternative therapeutic options in acromegalic patients after surgical failure or in those unsuitable for or unwilling to undergo surgery is still debated, as no single treatment modality seems to afford a cure in all patients. Medical treatment with long-acting SA is very effective in most patients (19), but it is expensive and life-long. The efficacy of RT, denied by some researchers (4, 20), is still controversial; its effects are very delayed and are often accompanied by a high incidence of side-effects (21, 22), such as hypopituitarism, cerebral necrosis, and a low possibility of damage to optic pathways, neuropsychological impairment and perhaps development of secondary tumors (13, 14, 23). Alternative modalities of radiation delivery, such as conformal radiotherapy by modified linear accelerators (24,

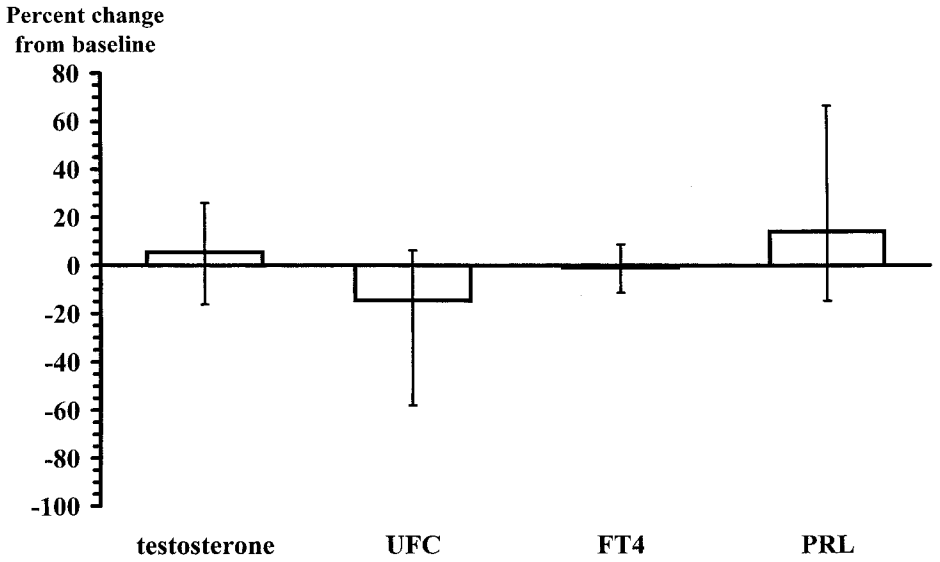

FIG. 4. Percent change from baseline (median, interquartile) at the last evaluation after GK for testosterone, UFC, free T_4 (FT_4), and PRL levels.

25) or particle accelerators (26), are still under evaluation or are not widely available, respectively. With these techniques the incidence of cerebral necrosis, neurocognitive dysfunctions, and optic damage is reported to be near nil.

In the present series GK produced safe GH levels and age-matched IGF-I normalization in about 25% of our patients within 5 yr. The doses employed have uniformly been decided in a defensive approach, backcalculating from the dose considered safe to the sensitive structures (in the order: optic pathways, lower stem, oculomotor nerves, and healthy pituitary) (27, 28) and covering the adenoma by whichever dose was allowed. As a progressive unrestrained decline in hormonal levels was observed in most patients, a more prolonged follow-up is needed to better evaluate the real effectiveness of GK in acromegaly.

A comparison with published results is difficult, because most series are either methodologically inhomogeneous or define cure by outdated or unspecified criteria (29–33). Only a few employ modern criteria of cure, as defined in the consensus conference (34), *i.e.* the achievement of basal GH levels less than 2.5 μg/liter and suppressibility less than 1 μg/liter after oral glucose load combined with normal age-matched IGF-I levels. Using these criteria, published results about GH and IGF-I normalization vary from 82% (14 of 17) described by Ikeda *et al*. (35) to 60% (6 of 10) by Jackson and Norén (36), 43% (39 of 91) by Vladyka *et al.* (37), and 29% (17 of 59) by Vance (38). Landolt and colleagues (39) reported a mean time of IGF-I normalization of 2.9 yr in keeping with our results. GK was used in most patients as a second step after surgical failure, *i.e.* in a selected population, that might not be representative of the previously untreated acromegalic patients. The decrease in GH and IGF-I levels in the three patients treated with GK as primary treatment did not differ from that in surgically treated patients. However, this sample is too small to draw any definitive conclusion.

For the comparison with results obtained by RT, it should be underlined that we did not perform a randomized comparative study of the two therapeutic modalities. The previous experience obtained by RT in acromegalic patients by the authors of this paper is not homogeneous; Epaminonda *et al.* (23) reported its effectiveness, but with the burden of hypopituitarism in a considerable portion of the series, whereas Cozzi and colleagues (20) observed its substantial failure, due perhaps to methodological differences in the irradiation procedure. It may be of interest that the percentage of patients who normalized IGF-I after a median follow-up similar to that of the present study (4–5 yr) was 24% in the case studies of Epaminonda *et al.* (23) (pretreatment GH, 20.2 μg/liter) and 6.7% in the case studies of Cozzi *et al.* (20) (pretreatment GH, 18 μg/liter). Only Landolt *et al.* (40) reported the direct comparison of the two techniques, showing that the percent decrease in GH/IGF-I values from baseline was steeper by GK compared with RT. It is fair to say that a correct comparison should be performed with modern techniques, allowing conformation and precise focusing of radiation on tumoral tissue.

In contrast with previous data obtained by RT, showing better outcome in acromegalic patients whose basal GH levels were lower (21, 23), in this series the control of hormonal hypersecretion was not dependent on basal GH values.

The observation that four patients reached safe GH levels, but still had high IGF-I concentrations, is in keeping with several previous findings after RT (4, 23) and might be explained by the persistence of a lower, but continuously released, tonic GH secretion capable of inducing an exaggerated stimulation of hepatic IGF-I synthesis (41, 42).

No difference in the outcome was observed between the patients who received SA at the time of GK application and those who did not, in contrast with Landolt *et al.*'s suggestion of a radioprotective effect of octreotide (43), confirmed later in the retrospective evaluation of another series of patients submitted to RT (20). However, this study was not designed as a prospective randomized one and, even if the two subgroups seem balanced for age, hormonal levels, and tumor volume, a definitive answer to the issue of whether it is better to administer ionizing radiation to resting or active cells cannot be given.

In our series GK was very effective in controlling tumor

mass, as demonstrated by the lack of further growth of the adenoma in all patients and by the outstanding shrinkage in most. The control of tumoral growth was already reported in virtually all acromegalic patients, with shrinkage in many (30, 31, 44, 45). The only exception was reported by Pan and colleagues (46), who observed a volumetric increase in the tumor in 3 of 65 patients. A word of caution about size reduction is mandatory. It cannot be ruled out that this effect may be linked to concomitant SA treatment carried on throughout the follow-up period in most patients. On the other hand, neuroradiological evaluation was always performed in the same conditions as those used for treatment withdrawal or its prolongation, to minimize drug interference. Moreover, several reports showed that tumor shrinkage is much less evident or negligible in patients treated with SA after surgery compared with patients treated with these drugs as first line treatment (47).

The dissociation between the control of tumor growth and that of hormonal hypersecretion is well known. In fact, it has been reported (37, 48) that the dose of radiation to be administered to the tumor is different if the goal of therapy is to reverse an endocrinopathy or merely to halt growth.

Finally, we stress that the procedure seems safe: no major side-effect was observed, no visual impairment developed, and the occurrence of hypopituitarism was very rare. Limiting factors in the delivery of an ablative radiation dose include its proximity to the optic apparatus and the size of the tumor. To avoid visual impairment, the dose of radiation to the optic chiasm should not exceed 10 Gy, and our choice was in agreement with the most restrictive cut-off of 8 Gy to the visual pathways (27). Accordingly, pituitary tumors with suprasellar extension that abut the optic apparatus cannot receive a tumor ablative dose without the risk of compromising vision. The same restrictions do not apply to tumors extending laterally into the cavernous sinus, where cranial nerves III, IV, V, and VI are much less susceptible to radiation damage than is the optic nerve. In comparison with RT, GK permits conformation of the radiation to the tumor shape, thus limiting the radiation exposure of surrounding tissue. Literature data report the rare occurrence of visual damage (30, 49), which we did not observe, and the variable occurrence of hypopituitarism, ranging from less than 5% (37), concordant with us, to 10–29% (31, 38, 50). These differences may be explained by the neurosurgeon's expertise.

As for the development of secondary tumor, previously described as a rare event in the field of irradiation with RT (13, 14, 23), it has never been observed after GK, even after a follow-up longer than 30 yr (51).

Patients who previously underwent RT did not develop distinctive adverse effects; their hormonal pattern was similar to those of the remaining patients. Thus, previous unsuccessful RT does not seem to constitute a restriction to GK, as previously reported (37, 40).

In conclusion, our data show the effectiveness of GK in acromegalic patients, both on the control of hormonal hypersecretion and on tumoral mass. It appears to be at least as efficacious and probably safer than conventional RT.

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