CLINICAL STUDY

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

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Abstract

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

Design: Forty patients with Cushing's disease treated by GK were prospectively studied over a decade, with a mean follow-up of 54.7 months. Eleven of them were treated with GK as a primary treatment. **Methods:** Radiosurgery was performed at the Department of Functional Neurosurgery of Marseille, France, using the Leksell Gamma Unit B and C models. Median margin dose was 29.5 Gy. Patients were considered in remission if they had normalized 24-h free urinary cortisol and suppression of plasma cortisol after low-dose dexamethasone suppression test.

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

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

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Introduction

Adrenocorticotrophic hormone (ACTH)-dependent Cushing's syndrome may be caused by a pituitary corticotrope adenoma (Cushing's disease (CD), 80–85% of cases), by an extrapituitary tumor (ectopic ACTH syndrome), or very rarely by a corticotrophin-releasing hormone (CRH)-secreting tumor (ectopic CRH syndrome). When diagnosed, because of signs and symptoms of chronic endogenous glucocorticoid excess, most corticotrope adenomas are microadenomas (<10 mm in largest diameter). Complications of CD include hypertension, hypertrophic cardiomyopathy, diabetes, obesity, hyperlipidemia, osteoporosis, and cognitive alterations probably due to a diminished cerebral volume (1).

Transsphenoidal surgery is usually the first-line treatment of CD. In series reported by experienced surgeons, immediate success rate varies from 64 to 93% (2, 3). Recurrence, frequent 5–10 years after

surgery, occurs in 9–25% of cases (3). Various treatments for recurrence have been proposed, but each has specific risks: Nelson's syndrome after bilateral adrenalectomy (4) and hepatic cytolysis during medical treatment such as ketoconazole (5). Conventional radiotherapy leads to more than 80% of cure in most of the series published, but it tends to be less employed because of a number of adverse effects, including hypopituitarism, cranial nerve neuritis, visual-field defects, possible cognitive disturbances or increased cerebro-vascular disorders, radiation-induced gliomas, and delayed brain necrosis (6–10).

Radiosurgery is a neurosurgical technique using a source of ⁶⁰Cobalt, where narrow beams are delivered in a single session with stereotactic precision and accuracy in order to destroy or biologically modify a target without opening the skull and with minimal damage to the surrounding brain. The critical structures around the target are spared through the high conformity and anatomical selectivity of dose delivery. In contrast with

radiotherapy, which covers the lesion and the surrounding structures with a fractionated dose, stereotactic radiosurgery aims to minimize injury to the surrounding structures included in the field of irradiation by fractionation, creating a gradient of toxicity on the target cells and the normal tissue (biological selectivity). Moreover, the radiobiological effect of a single high dose is much higher than a fractionated treatment for slowly growing benign lesions like adenomas (11).

As reviewed elsewhere (12, 13), several authors have detailed their experience with gamma knife (GK) in CD. Endocrinological 'cure' rates varied from 17 to 83%, with highly heterogeneous criteria of remission, and most studies were based on short-term effects of GK (14–20).

The aim of the present study was to analyze our 10-year experience with GK in a single radiosurgical center either as first non-medical treatment or as an adjunctive treatment after transsphenoidal surgery for CD. We thus evaluated the clinical and hormonal outcome in 40 patients, with a mean follow-up of 54.7 months (median, 48 months; range, 12–120 months).

Patients and methods

Patients

A total of 43 patients with active CD were consecutively treated with GK between February 1993 and May 2003 at the Department of Functional Neurosurgery of the University Hospital La Timone (Marseille, France). The diagnosis of CD was based on the association of clinical features of the disease, elevated 24-h urinary free cortisol level (mean of three samplings), elevated morning serum cortisol, and ACTH levels with a lack of response to a standard low-dose dexamethasone suppression test (2 mg/day for 2 days), and appropriate response to a high-dose dexamethasone test (8 mg/day for 2 days) (1). In the absence of an unequivocal image of pituitary adenoma at magnetic resonance imaging (MRI) (see below), inferior petrosal sinus sampling was performed.

These patients had been referred from 15 centers in France and 1 in Luxemburg. Each center agreed to monitor the patients' outcome according to the standardized investigation described below. Immediate pre- and post-radiosurgical evaluations were performed in the same department of endocrinology in Marseille.

In the present study, we did not analyze data from three patients who were lost to follow-up. For data analysis, 40 patients were thus entered into this retrospective study. Twenty-nine of them were treated after unsuccessful transsphenoidal surgery. Two had also previously received conventional radiotherapy. Eleven patients received medical treatments before GK because of non-resectable adenomas (such as small intrasellar adenomas with laterosellar extension), contraindication (due to the patient's general condition), or refusal of surgery. Only one patient had two consecutive GK (patient 29; Table 2).

Clinical and hormonal evaluation

Each patient had a complete clinical and hormonal evaluation before GK in the Endocrinology Department of the Timone Hospital (Marseille, France) and ophthalmologic evaluation (visual acuity, visual field measurement, and Lancaster testing) in the same Hospital. Initial pre-GK levels of 0800 and 2000 h ACTH and cortisol, urinary free cortisol, insulin-like growth factor-I, prolactin, luteinizing hormone, follicle-stimulating hormone, testosterone or estradiol, thyroid-stimulating hormone (TSH), and free T3 and T4 were determined. The same hormonal evaluation was repeated in each center every 6 months during 2 years, and then yearly to monitor pituitary functions. A low-dose dexamethasone test was concomitantly performed to determine the efficiency of radiosurgery.

During follow-up, ACTH and cortisol levels were determined without any medical therapy or after at least 3 months of discontinuation of the treatment with anticortisolic drugs. All patients treated with anticortisolic drug were given ketoconazole. None of them received Op'DDD. All pre-GK evaluations were performed without any anticortisolic drug treatment. Patients were considered in remission if they had normalized 24-h urinary free cortisol with suppressible plasma cortisol level after low-dose dexamethasone suppression test. Those who were still on anticortisolic drugs were considered uncured. Patients who had bilateral adrenalectomy during follow-up ($n=5$) were considered uncured.

Gonadotrope deficiency was defined clinically and biologically: low plasma testosterone with non-elevated gonadotropin levels in men, amenorrhea with low plasma estradiol and low or normal gonadotropins in non-menopausal women, and a lack of increased gonadotropins in post-menopausal women. Normal values of testosterone, estradiol, and gonadotropins were defined in each investigation center varying with the kits used. Somatotrope deficiency was defined by subnormal response of GH to an insulin tolerance test (peak below 3.3 µg/l). The diagnosis of thyrotrope deficiency was based on low free T4 level with normal or diminished TSH. Hypopituitarism was evaluated every 6 months during 2 years, and then yearly, and was assessed in each center by the investigators. Pre- and immediate post-GK evaluations were indeed determined in the center of Marseille, France. All other determinations were performed in each of the 15 other centers using commercial kits and normal values for each laboratory were taken into account.

Neuroimaging and radiosurgical procedure

Application of the stereotactic frame was performed under local anesthesia on the morning of the procedure. Radiological stereotactic preoperative investigations systematically included an MRI and a CT scan in

order to verify the absence of distortion of the MR. The MR sequences were performed on a Siemens 1.5 T machine. The 3DT1 sequence (MPRage, 1.5 mm thickness) was associated to a T2 weighted coronal sequence (TurboSpin Echo, 2 mm thickness, 512×512) to optimize the visualization of the limits of the lesion and the surrounding critical structures in the cavernous sinus and to delineate the optic pathways.

For the radiosurgical procedure, the GK models B and C (robotized version) were used for the periods 1992–2000 and 2000–2003 respectively.

For the indication, the decision-making process included the endocrinologists, the neurosurgeon specialized in sellar region microsurgery, and the neurosurgeon specialized in radiosurgery. When possible, the exact contours of the target were precisely delineated at this stage. All radiosurgical planning procedures were conducted by the same neurosurgeon (J R). The dose planning was always multi-isocentric. The reference isodose at the margin was usually the 50% isodose. The prescribed margin dose varied according to several factors: tumor volume, distance to the visual pathways, age, and previous treatment with radiotherapy. In each case, marginal dose, dose and distance to the optic pathways, and dose to the brainstem and pituitary stalk were monitored and recorded.

Statistical analysis

Statistical Package for the Social Sciences (software version 13.0 for Windows XP, Chicago, IL, USA) was used for statistical analysis. Data were analyzed by parametric or non-parametric tests. Continuous data with normal distribution were analyzed by *t*-test, and those with uneven distribution by Mann–Whitney test. Categorical data were analyzed by Fischer's exact test. When necessary, one-way ANOVA test was performed. Longitudinal evaluations were performed by Kaplan–Meier method. All statistical tests were two-tailed, and $P < 0.05$ was considered significant.

Results

The patients were followed up for a mean period of 54.7 months (median, 48 months; range, 12–120 months).

Parameters of GK treatment

The margin dose ranged from 15 to 40 Gy (median 29.5 Gy). The dose delivered to the optic chiasm and nerves was < 8 Gy (median 3.6 Gy) with a distance to the chiasm from 2 to 6.8 mm (median 4 mm). The volume of the residue, or the adenoma in case of first non-medical treatment (target volume), ranged from 94 to 4300 mm³ (median 521 mm³). The dose to the brain stem ranged from 1 to 20.3 Gy (median 4.2 Gy). The dose to the stalk ranged from 2 to 20 Gy (median 8.25 Gy).

Efficacy of GK treatment

At the end of the study, 17 patients (42.5%) had normalized 24-h free urinary cortisol with suppression of plasma cortisol level after low-dose dexamethasone suppression test, after a mean time of 22 months (range 12–48 months) (Fig. 1). Individual data are presented in Tables 1 and 2. The patient who had two consecutive GK treatments was not in the remission group 48 months after the second treatment. The two patients previously treated by conventional radiotherapy were considered uncured as bilateral adrenalectomy was necessary 2 years after GK.

No significant difference was observed in sex ratio, median age, type of the adenoma before the first treatment (microadenoma or macroadenoma), localization of the adenoma (latero- or intrasellar), marginal dose, and length of the follow-up. Among the patients with uncertain target definition ($n = 5$), two were in the remission group.

Initial target volume before GK was significantly lower (443 vs 909.8 mm³, $P = 0.038$) in the remission than in the uncured group (Fig. 2). We found no significant difference between initial hormonal levels (298 vs 323 µg/24 h) between the two groups (Table 3). In contrast, we found a significant difference between patients who were on or off anticortisol drugs at the time of GK ($P = 0.02$). At the time of GK, 15 patients (37.5%) were treated with anticortisol drugs; only 3 of them (20%) were in remission after GK, whereas 12 patients (48%) in the group of 25 patients without medical therapy at the time of GK were considered in remission at the end of the study (Table 4).

Eleven patients had GK as a primary non-medical treatment. In Table 5 are presented the data on patients

Figure 1 Long-term effects of GK in Cushing's disease evaluated by Kaplan–Meier analysis: probability of being uncured as a function of time. Remission was based on the following criteria: normalized 24-h free urinary cortisol level and suppressible plasmatic cortisol level after low-dose dexamethasone suppression test.

Table 1 Characteristics of patients in remission ($n=17$).

	Sex/age (year)	Type/ localization	Primary/ adjunctive	24-h free urinary cortisol ($\mu\text{g}/24\text{ h}$)	Anticortisolic status	Margin dose (Gy)	Target volume (mm^3)	Follow-up/ time to remission (months)	Complication deficiency
1	F/50	M/LS	P	456	Off	35	278	84/24	
2	M/32	m/LS	A	230	Off	35	521.4	24/18	
3	F/35	m/BD	A	160	Off	25	777.2	30/30	
4	F/34	m/IS	P	92	Off	35	153.9	12/12	
5	F/71	M/LS	A	850	Off	20	898	72/30	
6	F/39	m/LS	A	308	Off	30	409.9	78/12	
7	F/46	M/LS	A	270	On	25	671	84/18	
8	M/59	M/BD	A	262	On	35	153.9	120/48	Panhypopit.
9	F/32	M/LS	A	98	Off	25	702.4	18/18	Panhypopit.
10	F/39	M/LS	A	175	Off	30	557.8	25/18	
11	F/43	m/LS	A	215	On	35	418.7	48/36	
12	M/43	M/LS	A	128	Off	15	462.6	60/12	
13	F/35	m/LS	P	929	Off	35	153.9	96/30	
14	F/48	m/LS	A	91	Off	30	169.6	120/12	
15	F/14	M/LS	A	310	Off	25	476.9	24/24	TSH, GH
16	M/42	M/LS	A	214	Off	30	409.9	48/18	
17	M/4	m/LS	A	280	Off	25	300.1	12/12	GH

Remission was based on the following criteria: normalized 24-h free urinary cortisol level and suppressible plasmatic cortisol level after low-dose dexamethasone suppression test. Patient characteristics include sex (F, female; M, male), age, initial type of the adenoma (M, macroadenoma larger than 10 mm; m, microadenoma smaller than 10 mm), localization of the adenoma (LS, laterosellar; IS, intrasellar; BD, bad definition), primary non-medical treatment (P) or adjunctive treatment (A), initial 24-h free urinary cortisol off anticortisolic drug, anticortisolic status: patients who were on anticortisolic drug at the time of GK were considered on treatment (On); untreated patients were considered off treatment (Off); dose to the margin (Gy), target volume (mm^3), length of follow-up and time to remission (months), and complication deficiency (type of new hormonal deficiency appearing after GK; panhypopit., panhypopituitarism).

Table 2 Characteristics of uncured patients ($n=23$).

	Sex/age (year)	Type/ localization	Primary/ adjunctive	24-h free urinary cortisol ($\mu\text{g}/24\text{ h}$)	Anticortisolic status	Margin dose (Gy)	Target volume	Follow-up (months)	Complication deficiency
18	F/44	M/LS	A	180	Off	25	766	12	
19	F/35	m/LS-IS	A	235	On	25	759.9	48	
20	F/39	M/LS	A	160	On	25	405	36	
21	F/33	M/LS	A	252	Off	25	731	24	
22	M/63	m/BD	P	184	On	35	594.7	84	
23	F/34	m/LS	P	8040	On	35	94.3	24	
24	F/55	M/LS	A	478	On	35	251.2	30	
25	M/23	M/LS	A	93	Off	20	1100	90	
26	F/18	m/LS	A	561	On	35	329.7	30	
27	F/29	M/LS	P	220	On	25	339.6	24	
28	F/49	M/LS	A	165	Off	35	706.5	120	
29	F/33	m/LS	A	530	On	25	1852	48	TSH
30	F/14	M/LS	A	848	On	25	4300	30	
31	F/50	m/IS	P	125	Off	30	132.2	60	
32	F/55	m/LS	P	191	Off	30	595.7	30	
33	F/24	m/BD	A	1040	On	30	403	96	Panhypopit.
34	F/63	m/LS	P	96	Off	35	132.1	84	
35	F/28	M/BD	A	450	On	15	1700	84	
36	M/26	m/LS	P	220	On	25	615.9	30	
37	F/37	m/LS	A	92	Off	40	110.9	48	
38	F/34	m/LS	A	640	Off	25	1700	48	
39	F/42	M/LS	P	240	Off	30	329.7	96	
40	F/76	M/LS	A	395	Off	25	2200	60	

Remission was based on the following criteria: normalized 24-h free urinary cortisol level and suppressible plasmatic cortisol level after low-dose dexamethasone suppression test. Patient characteristics include sex (F, female; M, male), age, initial type of the adenoma (M, macroadenoma larger than 10 mm; m, microadenoma smaller than 10 mm), localization of the adenoma (LS, laterosellar; IS, intrasellar; BD, bad definition; one patient had an intra- and laterosellar localization), primary non-medical treatment (P) or adjunctive treatment (A), initial 24-h free urinary cortisol off anticortisolic drug, anticortisolic status: patients who were on anticortisolic drug at the time of GK were considered on treatment (On); untreated patients were considered off treatment (Off); dose to the margin (Gy), target volume (mm^3), length of follow-up (months), and complication deficiency (type of new hormonal deficiency appearing after GK; panhypopit., panhypopituitarism).

Figure 2 Initial target volume and localization of the adenoma in patients in remission (left side, patients 1–17) and uncured (right side, patients 18–40). Remission was based on the following criteria: normalized 24-h free urinary cortisol level and suppressible plasmatic cortisol level after low-dose dexamethasone suppression test. Localization is represented by a lozenge when laterosellar, a circle when intrasellar, and a cross when uncertain. Target volume, mm³.

treated with GK as a primary or as an adjunctive treatment ($n=29$). GK as a primary treatment was more often used in microadenomas (73 vs 41%) than in macroadenomas (only three small enclosed macroadenomas were treated). Target volume was not significantly lower in the 'primary treatment' group (329 vs 836 mm³); marginal dose was significantly higher in the same group (32 vs 27.4 Gy, $P=0.03$). Rate of remission was not significantly different between both the groups at the end of the study (27 vs 48.3%).

Tolerance of GK treatment

At least one new pituitary deficiency was observed after GK in six patients (15%): TSH deficiency in two (during

Table 3 Comparison between in remission and uncured groups.

	In remission	Uncured	P
No. of patients	17 (42.5%)	23 (57.5%)	
Mean age (year)	39.2 (4–71)	39.3 (14–76)	0.98
Sex ratio (F/M)	12/5	20/3	0.20
Marginal dose (Gy)	28.8 (15–35)	28.5 (15–40)	0.86
Micro-/macroadenoma	8/9	12/11	0.75
Tumor extension			0.83
Laterosellar	14 (82%)	19 (82%)	
Suprasellar	0	0	
Intrasellar	1	2	
Bad definition	2	3	
Target volume (mm ³)	443 (153.9–898)	909.8 (94.3–4300)	0.038*
Initial 24-h urinary cortisol (μg/24 h)	298 (91–850)	323 (92–8040)	0.76
Patients on anticortisol drug	3 (17.6%)	12 (52%)	0.025*
Follow-up (months)	56.2 (12–120)	53.7 (12–120)	0.81

Remission was based on the following criteria: normalized 24-h free urinary cortisol level and suppressible plasmatic cortisol level after low-dose dexamethasone suppression test. Extreme values are given in brackets. Sex ratio is presented as number of female (F)/number of male (M) patients. Tumor extension was determined by pretreatment MRI as detailed in Patients and methods. One patient in the uncured group had a latero- and intrasellar localization. Percentages indicate the proportion of patients in each subgroup. *Significant difference; $P<0.05$ was considered significant.

the first year after GK), GH deficiency in two (4 and 7 years after GK), and complete hypopituitarism in three (7 years after GK for two patients and 8 years after GK). Note that four out of these six patients were treated with the first generation dose planning system (Kula system, Elekta Instrument AB, Stockholm, Sweden). The six patients were treated with GK as an adjunctive treatment ($P=0.012$ compared with primary treatment group). The mean margin dose for these six patients was 29.1 vs 28.5 Gy for patients without adverse effects (not statistically significant). For two out of the three patients who had complete hypopituitarism, target definition was uncertain and tomosellar radiosurgery was performed due to the severity of the disease. Two ophthalmic complications were observed: patient 16 presented a transient ptosis of the right eyelid, probably explained by radiation-induced oculo-motor neuropathy although MRI showed no changes of the intracavernous remnant of the adenoma. Patient 29 presented partial ophthalmoplegia 1 year after her first session of GK: ophthalmoplegia became definitive after the second session of GK. Ophthalmoplegia was attributed to radiation-induced neuropathy of the external oculo-motor nerve despite unchanged MRI. Only a few patients had other transient adverse effects, including headaches or vomiting.

Discussion

Even if transsphenoidal surgery remains the first-line treatment of CD, definitive surgical cure for locally invasive adenomas is infrequent due to early failure or late recurrence of the disease. The morbidity associated with CD may be severe with multiple organ systems affected; the mortality rate associated with this syndrome, if untreated, has been reported to be as high as 50% within 5 years, requiring effective adjunctive treatment be performed (1).

With GK, more than 40% of our patients were in remission based on 24-h free urinary cortisol and suppressible plasma cortisol levels at low-dose dexamethasone suppression test after a mean time of 22 months. We chose these criteria of remission based on the latest consensus conference on the diagnosis of CD (21), even though recent studies showed the equal value of salivary cortisol level in the diagnosis of CD (22, 23). Only two patients considered uncured had a follow-up lower than the mean time to remission: a longer follow-up would thus be useful to better evaluate the effectiveness of GK especially for these patients. In a recent review of currently published series, 58% of 208 patients with CD treated by GK were considered in remission with a mean follow-up of 54.6 months (12). These results differ from ours. However, as mentioned in another recent review (13), criteria for remission were very different, including normalization of 24-h free urinary cortisol (UFC), or of 0800 ACTH and cortisol levels, or simply of 'hormonal levels'. Moreover, patients

Table 4 Comparison between patients with or without anticortisolic drugs at the time of gamma knife.

	Anticortisolic treatment	No anticortisolic treatment	P
No. of patients	15	25	
Mean age (year)	36.4 (18–59)	40.9 (4–76)	0.37
Sex ratio (F/M)	12/3	20/5	1
Margin dose (Gy)	28.7 (15–35)	28.6 (15–40)	0.97
Micro-/macroadenoma	8/7	12/13	0.74
Target volume (mm ³)	859 (94.3–4300)	610 (153.9–2200)	0.33
Initial 24-h free urinary cortisol (µg/24 h)	384.2 (160–8040)	269.4 (91–929)	0.17
follow-up (months)	54.4 (24–120)	55 (12–120)	0.95
In remission	3/15	14/25	0.025*
Uncured	12/15	11/25	0.025*

Remission was based on the following criteria: normalized 24-h free urinary cortisol level and suppressible plasmatic cortisol level after low-dose dexamethasone suppression test. Extreme values are between brackets. Sex ratio is presented as number of female (F)/number of male (M) patients. Percentages indicate the proportion of patients in each subgroup. *Significant difference; $P < 0.05$ was considered significant.

were sometimes treated three or four times with GK before being considered cured (18).

The status of the five patients treated with bilateral adrenalectomy in our series is difficult to evaluate: we considered them as uncured, because most of them were operated on at least 24 months after unsuccessful GK, which is more than our mean time to remission. Nevertheless, one patient had a bilateral adrenalectomy only 12 months after GK because of persistently aggressive signs of CD. None of these five patients presented with increased volume of the tumor remnant, which might have been suggestive of Nelson's syndrome.

Our mean time to remission was 22 months, which is consistent with the previous reports: 6–36 months after GK (12). In most published series of CD patients treated with conventional radiotherapy (6, 8, 9), remission usually started after 9 months of treatment, and most patients were in remission within 5 years, suggesting that GK may allow faster remission than conventional radiotherapy in CD.

In line with other series (17, 18), initial UFC levels were not correlated with the outcome of GK. Interestingly, however, tumor volume was significantly higher in the uncured group than in the remission group. Indeed, as shown in Fig. 2, smaller tumor remnants were more likely to be efficiently treated than larger targets except when tomosellar irradiation was purposely performed in lesions uncertainly defined at MRI.

In acromegaly, incidence of antisecretory drugs at the time of GK has been a matter of controversy. Some studies suggested that the pre-GK somatostatin agonist (24) treatment had a radioprotective effect (24) and some did not (25, 26). We found a significantly higher proportion of uncured patients in the group with anticortisolic drug at the time of GK than in the group without medical therapy. This observation was indeed not explained by a difference in initial tumor volume, type of adenoma (micro- or macroadenoma), margin dose, baseline UFC, or duration of follow-up. It remains speculative whether this might be explained by the fact that clinically more aggressive tumors requiring medical treatment were less likely to respond to GK.

Note that no study before ours evaluated the incidence of anticortisolic drugs in patients treated with GK, making difficult any comparison with literature. Moreover, ketoconazole has mainly peripheral effects and to our knowledge, only one *in vitro* study described central effects of ketoconazole on ACTH secretion (27).

To our knowledge, only few studies have included patients treated as a primary and as an adjunctive treatment. We observed only 27% of patients cured in the 'primary treatment' group versus 48% in the 'adjunctive treatment' group, suggesting that GK may be more effective as an adjunctive treatment. Such a difference that did not reach statistical significance may be explained by selection of better visualized lesions in the surgical group although this was not reflected in the comparison of tumor volumes and target definitions at MRI between both the groups.

During long-term follow-up, our patients showed no increase in tumor volume, as observed in other series (14, 15, 17). We did not systematically monitor tumor size as the treatment was not primarily aimed at reducing target volume, which was most of the time a

Table 5 Comparison between gamma knife (GK) as a primary non-medical treatment (without previous surgical treatment) and as an adjunctive treatment (after surgical treatment).

	Primary treatment	Adjunctive treatment	P
No. of patients	11/40 (27.5%)	29/40 (72.5%)	
Mean age (year)	43.7 (26–63)	37.6 (4–76)	0.25
Sex ratio (F/M)	9/2	23/6	0.86
Margin dose (Gy)	32 (25–35)	27.4 (15–40)	0.032*
Micro-/macroadenoma	8/3	12/17	0.076
Target volume (mm ³)	329 (94.3–615.9)	836 (110.9–4300)	0.072
Initial 24-h free urinary cortisol (µg/24 h)	310 (92–8040)	308 (91–1050)	0.38
follow-up (months)	56.4 (12–96)	54 (12–120)	0.82
Anticortisolic drug at the time of GK	4/11 (36.3%)	11/29 (37.9%)	0.92
In remission	3/11 (27%)	14/29 (48.3%)	0.23
Uncured	8/11 (73%)	15/29 (51.7%)	0.23

Extreme values are between brackets. Sex ratio is presented as number of female (F)/number of male (M) patients. Percentages indicate the proportion of patients in each subgroup. *Significant difference; $P < 0.05$ was considered significant.

small remnant or a small enclosed macroadenoma. According to a recent review, tumor growth control was obtained in 86–100% in all but one series (13).

GK induced few complications in our patients: only three presented complete hypopituitarism, but two of them had uncertain target definition and needed totosellar radiotherapy. GK more precisely localizes tumors and neural structures, but it requires accurate definition of the target volume to avoid complications. Six patients (15%) presented at least one new pituitary hormone deficiency after GK radiosurgery. All of them were treated with GK radiosurgery as an adjunctive treatment. A significant difference was observed between both the groups in terms of adverse effects ($P=0.012$). As patients treated with radiosurgery as an adjunctive treatment were more often cured than those treated as a primary treatment, a correlation indeed seems to exist between hypopituitarism rate and remission rate. As a group, operated patients had a significantly larger target volume than patients treated first-line by GK. A larger target volume has the inconvenient of being more likely to include both more of the normal pituitary tissue leading to partial hypopituitarism and more of the adenomatous tissue that often lies at the periphery of the lesion visualized on MRI. The rate of hypopituitarism observed in our study (15%) is consistent with the previously published data: an incidence of hypopituitarism ranging from 4 to 55% was observed in different series (16, 17, 19, 20). This percentage decreases to 10% if we exclude two patients treated with totosellar radiotherapy on the basis of a balance between the complications of an invasive CD, and the high probability of panhypopituitarism. Additionally, one of the patients with a deficit had received fractionated radiotherapy before GK. In the study of Hoybye *et al.* (18), 66% of the patients presented hypopituitarism, but these patients were sometimes treated twice or more in the pre-CT and MRI era of radiosurgery, probably leading to imprecise target definition. Indeed, the use of GK should be limited to patients in whom a clear target definition is possible. In contrast, in case of imprecise target definition, decision of treating by GK radiosurgery or conventional radiotherapy should be precisely evaluated. The only patient of our series treated twice was not cured and presented a partial hypopituitarism 1 year after GK. Two of our patients treated with the first generation dose planning system presented oculo-motor complications; none had a visual deficit in spite of the high level of energy used (median 29.5 Gy) and the close relationship to the optic pathways. In all of our patients, as previously recommended (28), the dose to the chiasm was always inferior to 8 Gy. We think that the two ophthalmic complications described in our study were due to radiation-induced neuropathies in the intracavernous portion of the nerves, which was part of the tumor target. A recent review (13) reports an incidence of cranial neuropathy of 1.3% in 1567 patients.

Neuropathies concerned intracavernous portions of the nerves. Half of these neuropathies were transient.

In the series from our center (25) and from other authors, GK appeared more effective in CD than in acromegaly. In our patients, as in another recently published series of acromegalic patients treated with GK, remission rate was about 20% with a follow-up of about 48 months (25, 26). In the present study in CD, the mean time to remission was 22 vs 36 months in our patients with acromegaly (25). Nevertheless, it does not appear that somatotrope cells are less radiosensitive than corticotropes since higher margin doses were used to treat patients with Cushing's disease in our study. Note that for both conventional radiotherapy and radiosurgery, previous studies found a faster rate of remission in CD than in acromegaly (3–24 vs 6–36 months respectively) (12).

With an overall remission rate of more than 40%, and a remission rate of 48% in previously operated patients, stereotactic radiosurgery can be considered an effective treatment in CD, especially for recurrent CD. Comparison with other treatments is difficult because various criteria of remission were used or insufficient data were available in the previous studies: antihypocortisolic drugs, like ketoconazole or mitotane (29, 30), have a wide range of efficacy, but they expose patients to dangerous hepatic cytolysis (5). The efficacy of glitazones is still discussed, due to several conflicting studies: pioglitazone yielded disappointing results, while rosiglitazone normalized UFC in 6 out of 14 patients with CD (31). Studies on long-term effects with strict criteria of remission would be helpful to determine the real efficiency of these drugs. Conventional radiotherapy seems to be more successful than stereotactic radiosurgery, but its major drawback is to induce hypopituitarism in virtually all patients (6–10).

To conclude, as an adjunctive treatment, GK allowed remission after an average of 22 months in about 50% of our patients, with the advantage of inducing fewer adverse effects. GK thus represents a valuable option for the treatment of patients with CD after unsuccessful transsphenoidal surgery, in well-defined indications: small post-surgical remnants with a good target definition, sufficiently distant from the optic chiasm.

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References

- Plotz CM, Knowlton AI & Ragan C. The natural history of Cushing's syndrome. *American Journal of Medicine* 1952 **13** 597–614.
- Hammer GD, Tyrrell JB, Lamborn KR, Applebury CB, Hannegan ET, Bell S, Rahl R, Lu A & Wilson CB. Transsphenoidal microsurgery for Cushing's disease: initial outcome and long-term results. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 6348–6357.
- Laws ER, Reitmeier M, Thapar K & Vance ML. Cushing's disease resulting from pituitary corticotrophic microadenoma. Treatment results from transsphenoidal microsurgery and gamma knife radiosurgery. *Neurochirurgie* 2002 **48** 294–299.
- Assie G, Bahurel H, Bertherat J, Kujas M, Legmann P & Bertagna X. The Nelson's syndrome... revisited. *Pituitary* 2004 **7** 209–215.
- Zollner E, Delpont S & Bonnici F. Fatal liver failure due to ketoconazole treatment of a girl with Cushing's syndrome. *Journal of Pediatric Endocrinology and Metabolism* 2001 **14** 335–338.
- Ahmed SR, Shalet SM, Beardwell CG & Sutton ML. Treatment of Cushing's disease with low dose radiation therapy. *British Medical Journal (Clinical Research Ed.)* 1984 **289** 643–646.
- Little MD, Shalet SM, Beardwell CG, Robinson EL & Sutton ML. Radiation-induced hypopituitarism is dose-dependent. *Clinical Endocrinology (Oxf)* 1989 **31** 363–373.
- Tran LM, Blount L, Horton D, Sadeghi A & Parker RG. Radiation therapy of pituitary tumors: results in 95 cases. *American Journal of Clinical Oncology* 1991 **14** 25–29.
- Tsang RW, Brierley JD, Panzarella T, Gospodarowicz MK, Sutcliffe SB & Simpson WJ. Role of radiation therapy in clinical hormonally-active pituitary adenomas. *Radiotherapy and Oncology* 1996 **41** 45–53.
- Estrada J, Boronat M, Mielgo M, Magallon R, Millan I, Diez S, Lucas T & Barcelo B. The long-term outcome of pituitary irradiation after unsuccessful transsphenoidal surgery in Cushing's disease. *New England Journal of Medicine* 1997 **336** 172–177.
- Jalali R, Brada M, Perks JR, Warrington AP, Traish D, Burchell L, McNair H, Thomas DG, Robinson S & Johnston DG. Stereotactic conformal radiotherapy for pituitary adenomas: technique and preliminary experience. *Clinical Endocrinology (Oxf)* 2000 **52** 695–702.
- Brada M, Ajithkumar TV & Minniti G. Radiosurgery for pituitary adenomas. *Clinical Endocrinology (Oxf)* 2004 **61** 531–543.
- Laws ER, Sheehan JP, Sheehan JM, Jagnathan J, Jane JA Jr & Oskoui R. Stereotactic radiosurgery for pituitary adenomas: a review of the literature. *Journal of Neuro-Oncology* 2004 **69** 257–272.
- Thoren M, Hoybye C, Grenback E, Degerblad M, Rahn T & Hulting AL. The role of gamma knife radiosurgery in the management of pituitary adenomas. *Journal of Neuro-Oncology* 2001 **54** 197–203.
- Sheehan JM, Vance ML, Sheehan JP, Ellegala DB & Laws ER Jr. Radiosurgery for Cushing's disease after failed transsphenoidal surgery. *Journal of Neurosurgery* 2000 **93** 738–742.
- Petrovich Z, Yu C, Giannotta SL, Zee CS & Apuzzo ML. Gamma knife radiosurgery for pituitary adenoma: early results. *Neurosurgery* 2003 **53** 51–59 (discussion 59–61).
- Kobayashi T, Kida Y & Mori Y. Gamma knife radiosurgery in the treatment of Cushing disease: long-term results. *Journal of Neurosurgery* 2002 **97** 422–428.
- Hoybye C, Grenback E, Rahn T, Degerblad M, Thoren M & Hulting AL. Adrenocorticotrophic hormone-producing pituitary tumors: 12- to 22-year follow-up after treatment with stereotactic radiosurgery. *Neurosurgery* 2001 **49** 284–291 (discussion 291–282).
- Hentschel SJ & Mccutcheon IE. Stereotactic radiosurgery for Cushing disease. *Neurosurgical Focus* 2004 **16** E5.
- Feigl GC, Bonelli CM, Berghold A & Mokry M. Effects of gamma knife radiosurgery of pituitary adenomas on pituitary function. *Journal of Neurosurgery* 2002 **97** 415–421.
- Arnaldi G, Angeli A, Atkinson AB, Bertagna X, Cavagnini F, Chrousos GP, Fava GA, Findling JW, Gaillard RC, Grossman AB, Kola B, Lacroix A, Mancini T, Mantero F, Newell-Price J, Nieman LK, Sonino N, Vance ML, Giustina A & Boscaro M. Diagnosis and complications of Cushing's syndrome: a consensus statement. *Journal of Clinical Endocrinology and Metabolism* 2003 **88** 5593–5602.
- Trilck M, Flitsch J, Ludecke DK, Jung R & Petersenn S. Salivary cortisol measurement – a reliable method for the diagnosis of Cushing's syndrome. *Experimental and Clinical Endocrinology and Diabetes* 2005 **113** 225–230.
- Yaneva M, Mosnier-Pudar H, Dugue MA, Grabar S, Fulla Y & Bertagna X. Midnight salivary cortisol for the initial diagnosis of Cushing's syndrome of various causes. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 3345–3351.
- Landolt AM, Haller D, Lomax N, Scheib S, Schubiger O, Siegfried J & Wellis G. Octreotide may act as a radioprotective agent in acromegaly. *Journal of Clinical Endocrinology and Metabolism* 2000 **85** 1287–1289.
- Castinetti F, Taieb D, Kuhn JM, Chanson P, Tamura M, Jaquet P, Conte-Devolx B, Regis J, Dufour H & Brue T. Outcome of gamma knife radiosurgery in 82 patients with acromegaly: correlation with initial hypersecretion. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 4483–4488.
- Attanasio R, Epaminonda P, Motti E, Giugni E, Ventrella L, Cozzi R, Farabola M, Loli P, Beck-Peccoz P & Arosio M. Gamma-knife radiosurgery in acromegaly: a 4-year follow-up study. *Journal of Clinical Endocrinology and Metabolism* 2003 **88** 3105–3112.
- Stalla GK, Stalla J, Loeffler JP, Von Werder K & Muller OA. Pharmacological modulation of CRH-stimulated ACTH secretion by ketoconazole. *Hormone and Metabolic Research. Supplement Series* 1987 **16** 31–36.
- Tishler RB, Loeffler JS, Lunsford LD, Duma C, Alexander E III, Kooy HM & Flickinger JC. Tolerance of cranial nerves of the cavernous sinus to radiosurgery. *International Journal of Radiation Oncology, Biology, Physics* 1993 **27** 215–221.
- Sonino N, Boscaro M, Paoletta A, Mantero F & Ziliotto D. Ketoconazole treatment in Cushing's syndrome: experience in 34 patients. *Clinical Endocrinology (Oxf)* 1991 **35** 347–352.
- Sonino N, Boscaro M, Merola G & Mantero F. Prolonged treatment of Cushing's disease by ketoconazole. *Journal of Clinical Endocrinology and Metabolism* 1985 **61** 718–722.
- Ambrosi B, Dall'asta C, Cannavo S, Libe R, Vigo T, Epaminonda P, Chiodini I, Ferrero S, Trimarchi F, Arosio M & Beck-Peccoz P. Effects of chronic administration of PPAR-gamma ligand rosiglitazone in Cushing's disease. *European Journal of Endocrinology* 2004 **151** 173–178.

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