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Gamma Knife surgery for recurrent or persistent Cushing disease: long-term results and evaluation of biological effective dose in a series of 26 patients

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Summary

INTRODUCTION: Here we report long-term results after stereotactic radiosurgery (SRS) with Gamma Knife (GKRS) for Cushing disease. We further evaluated the potential role of the biological effective dose (BED) in the cure of this disease.

METHODS: A retrospective review of a prospectively collected database (n = 26) was undertaken at Lille University Hospital, France. The mean follow-up period was 66 months (median 80, range 19–108). The mean marginal prescribed dose was 28.5 Gy (median 27.5, range 24–35) and the mean BED was 208.5 $Gy_{2.47}$ (median 228.1, range 160–248). We divided patients with endocrine remission into a high BED group (160–228 $Gy_{2.47}$, n = 6) and a low BED group (228–248 $Gy_{2.47}$, n = 12).

RESULTS: Eighteen (69.2%) patients had endocrine remission in the absence of any pharmacological therapy after a mean of 36 months (median 24, range 6–98). The actuarial probability of endocrine remission was 59% at 3 years and 77.6% at 7 years, which remained stable up to 10 years. There was a tendency to a higher overall probability of biological remission associated with higher BED values (77% versus 66% at last follow-up), although this did not reach statistical significance. Of note, the numbers of patients reflecting this actuarial probability at 12, 24, 36, 51 and 96 months were 21, 15, 11, 7 and 3, respectively. Tumour control was achieved in all cases (mean decrease in size for patients experiencing one was 29.4%, range 0–100%). Seven patients developed new pituitary insufficiency after GKRS.

CONCLUSONS: Gamma Knife radiosurgery offers high rates of tumour control and endocrine remission on a long-term basis for ACTH-secreting pituitary adenomas. In this small series, higher BED values appeared to be associated with better endocrine remission rates. Owing to the limited sample size, such results should be validated in a larger cohort.

Introduction

Cushing disease is a severe endocrine entity, which is generated by a corticotroph pituitary adenoma resulting in excessive adrenocorticotrophic hormone (ACTH) secretion. This disorder accounts for approximately 70% of endogenous hypercortisolism [1] and is associated with relevant morbidity and mortality [2]. The incidence of Cushing disease is approximately 1.2–2.4 per million per year [3].

The clinical picture is related to the disruption of the hypothalamus-pituitary-adrenal circuit, which increases circulating serum and urinary cortisol levels and disrupts the cortisol circadian rhythm [1, 2]. Major comorbidities include systemic arterial hypertension, diabetes mellitus, dyslipidaemia, osteoporosis, depression and infertility [1].

Primary treatment is microsurgical resection of the pituitary adenoma, which results in disease remission in approximately 50–90% of cases [4, 5], with relapse in around 13% during the first 10 years after microsurgery [6]. Microsurgical resection can be associated with complications including, but not limited to, damage to the optic apparatus, carotid artery, cavernous sinus and its components, and cerebrospinal fluid (CSF) leakage [7, 8]. Persistent and/or recurrent Cushing disease requires further treatment, including medical therapy, radiation [9–11] and/or adrenal surgery [12, 13].

Single-fraction stereotactic radiosurgery (SRS) and particularly Gamma Knife radiosurgery (GKRS) has been re-

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ported as safe and effective for ACTH-secreting pituitary adenomas [14–17]. The tumour control rate ranges between 83.3% and100%, with a rate of biological remission of between 17% and 87% [18]. Adverse radiation effects may include visual impairment (0–5.5%) and hypopituitarism (0–66%) [18]. The unique steep gradient of GKRS is particularly useful in delivering high doses of irradiation on small to medium size residual or recurrent ACTH-secreting pituitary adenomas. It has been classically considered that functional pituitary adenomas should benefit from higher doses of irradiation, the former being associated with a higher rate of biological remission [18]. More recently, biological effective dose (BED) emerged as a significant parameter for single fraction GKRS in functional indications [19], as being more predictive than the prescribed dose for safety and efficacy. This parameter incorporates, beside the dose factor, a time correction, which aims to take account of DNA repair during irradiation [19].

Here we report our long-term results for patients with recurrent and/or persistent Cushing disease treated by GKRS at our institution. We further evaluated whether BED could play a more significant role than the prescribed dose in biological remission on the basis of very long-term follow-up [20–22]. Our hypothesis was that BED could be a better predictor than the marginal prescribed dose for endocrine remission after single-fraction GKRS (Lille University Hospital, France). This assumption was based on previously published data. In particular, for trigeminal neuralgia, Tuleasca et al. [22] showed that safety and efficacy of GKRS was better predicted by BED than by the physical dose in a large cohort of 408 cases. Recently, we suggested that BED could be a better predictor for endocrine remission than the marginal prescribed dose in acromegaly [23]. Furthermore, we evaluated a large cohort of 149 patients with arteriovenous malformations treated with single-fraction, first intention GKRS [24]. In that cohort, BED and treatment time were the only statistically significant factors for arteriovenous malformation obliteration, whereas the marginal dose prescribed was not.

Methods

Study design and patient selection

The study was designed as a retrospective, nonrandomised, historical cohort. A case report form was created for each patient and prospectively filled in. Data were retrospectively analysed. The Lille University Hospital Ethics Committee approved our study.

All cases were treated in Lille University Hospital (CHU Roger Salengro), France between August 2004 and February 2013. Data were initially analysed in Lille. Biological effective dose was calculated by the co-first author (CT) in Lausanne, Switzerland, using the particular details of beam-on time and marginal prescribed dose.

We included cases with demonstrated endocrine evidence for Cushing disease, based upon serum cortisol, ACTH and 24-hour urinary free cortisol (UFC) levels, and with no indication for further surgery. Patients with less than 12 months follow-up were excluded. Neuroradiological assessment included brain magnetic resonance imaging (MRI) for all patients, which confirmed the presence of a pituitary adenoma.

Postoperative residual/recurrent tumour volumes (before SRS) were measured either by using the Leksell Gamma Plan station or by the referring neuroradiologist in the respective French centres.

More than half of the patients had cavernous sinus residual tumour, which is associated with higher surgical risks if radical resection is preferred [25]. Moreover, the residual or recurrent tumour volumes were compatible with single-fraction GKRS. There was a multidisciplinary discussion both in the hospital referring the patients for GKRS and in our hospital, to evaluate the feasibility of GKRS versus another surgical exploration. Before being admitted for GKRS in the setting of persistent or recurrent Cushing disease, repeat adenomectomy was evaluated as a first therapeutic option. However, all patients in the present series had had at least one surgery (n = 21), and a minority had had two procedures (n = 5). Taking into account the anatomical location, the volume and the previous surgical status, the decision for GKRS had been made.

Primary and secondary aim

The primary aim was tumour control. The secondary aim was endocrine remission in the absence of any pharmacological treatment. We further evaluated whether BED could play a role in endocrine remission.

Assessment before Gamma Knife radiosurgery

The assessment before GKRS encompassed basic demographic data, as well as necessary endocrinological assessment data, including 24-hour UFC, ACTH, free thyroxine, thyroid-stimulating hormone, prolactin, follicle-stimulating hormone, luteinising hormone, growth hormone, serum cortisol, testosterone in men, oestradiol (as well as menstrual history) in women, and a basic metabolic panel. No patient discontinued treatment with antisecretory drugs (e.g., ketoconazole) at the time of GKRS.

In all patients, a low-dose dexamethasone suppression test was used to confirm the diagnosis of active Cushing disease. The UFC was used to evaluate the results of GKRS.

Biological assessment after Gamma Knife radiosurgery

The specific outcomes evaluated after GKRS were tumour control, endocrine remission, pituitary insufficiency and potential visual status changes. The UFC was used to evaluate the results of GKRS. Remission was defined as a normal 1-mg dexamethasone suppression test and 24-hour UFC in two consecutive samples. Biological assessment took place at 6 months and 1 year, and annually thereafter.

Radiosurgery technique

Gamma Knife radiosurgery was performed using Leksell Gamma Knife® 4C (LGK, Elekta Instruments AB, Sweden). The Leksell G frame was placed under local anaesthesia. Brain MRI and computed tomography were done routinely. The MR sequences included thin slices (1 mm) T1 MPRAGE, with additional T2 and T1 fat suppression through the sellar region.

We usually prescribe 25–30 Gy at the margin in secreting pituitary adednomas whenever feasible. We consider this as the current standard of care. Limitations to prescription of such doses are mainly related to the optic apparatus, and

the distance between this and the tumour. We restrict less the dose received by the pituitary stalk, as in our view biological remission is more important than the appearance or not of pituitary insufficiency. The limit of doses to the optic apparatus has been considered a maximum of 8 Gy, as suggested in a historical series (please see the discussing section). However, on the basis of recent publications, in exceptional cases we have considered maximum doses to the optic apparatus of up to 10 or even 12 Gy [26].

Our strategy was to prescribe, whenever possible, high doses of radiation to the tumour. However, during treatment planning, we paid close attention to the maximum dose received by the optic apparatus, which was always extracted from the dose-volume histograms. In this cohort the doses received by the pituitary stalk and by the pituitary gland were not calculated at the time of GKRS.

Biological effective dose calculation

The BED was calculated using a simplified approach, similar to that described by Jones and Hopewell [19], taking into account the beam-on time and the prescribed dose. This approach is considered the "basic BED model", as described by several authors in the literature. By convention, we have considered the unit for BED measurement as being $Gy_{2.47}$, to differentiate it from the unit measurement for the dose (Gy), as previously suggested [22].

The mean BED received by the tumour was 208.5 $Gy_{2.47}$ (median 228.1, range 160–248). We also computed the mean BED received by the pituitary stalk, which was 86.7 $Gy_{2.47}$ (median 31.5, range 25.5–228.7). We divided patients with endocrine remission into a high BED group (H-BED, 160–228 $Gy_{2.47}$, n = 6) and a low BED group (L-BED, 228–248 $Gy_{2.47}$, n = 12). The two groups did not differ in pretherapeutic UFC levels or range of prescribed dose.

Patient follow-up after radiosurgery

Clinical and radiological follow-up were at 6 months and 1 year, and annually thereafter. The data were collected by one of the first authors (AB), who travelled to each referral centre outside Lille to collect the missing data in cases where the patient's return to our centre was not possible, mainly because of the distance.

Tumour control was defined as stability or decrease in volume after GKRS.

Statistical analysis

Statistical testing was performed using STATA 14 (StataCorp, College 109 Station, Texas). Descriptive statistics were reported as proportion/frequency for categorical data and mean, median and range for continuous variables. Odds ratios were further evaluated as an association between an outcome and a treatment/exposure. Variables assessed in univariate models included age, sex, baseline UFC (24 hours) and serum cortisol levels. Because of the insufficient sample size no multivariable analysis was performed.

For biological control and pituitary insufficiency after GKRS, survival over time was examined using the Kaplan-Meier method. Patients were censored at the time of cure (for biological control) or appearance of insufficiency, or otherwise at last follow-up.

The prescribed dose and BED were assessed using both continuous and binary data modelling techniques, with dichotomisation thresholds derived from received operating characteristic (ROC) tables and the maximum point of (sensitivity-(1-specificity)).

Results

Basic demographic data are presented in table 1 and dosimetric data in table 2.

The mean follow-up period was 66 months (median 80, range 19–108). The mean duration between surgery and GKRS was 60.8 months (median 84.6, range 11–182.5). No patient stopped antisecretory medication before GKRS (table 1).

The mean marginal prescription dose was 28.5 Gy (median 27.5, range 24–35; table 2). The mean target volume was 0.705 cc (median 0.110, range 0.090–3.7). The mean maximum dose received by the optic apparatus was 5.3 Gy (median 1.1, range 1–12.4). The mean maximum dose received by the pituitary stalk was 13.5 Gy (median 6.3, range 2.7–24.4), the former being collected retrospectively.

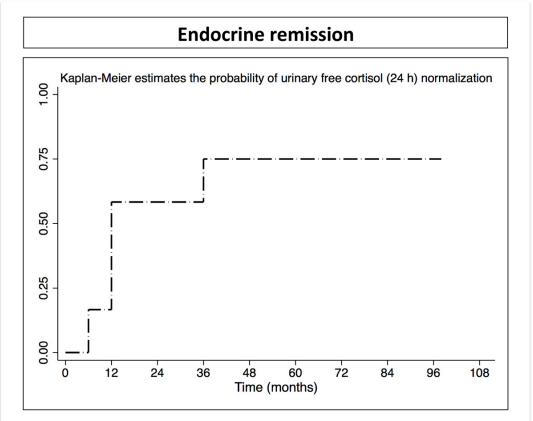
Tumour control after Gamma Knife radiosurgery

Tumour control was achieved in all cases (mean decrease in size 29.4%, range 0–100%).

Biological remission in the absence of any pharmacological treatment

Eighteen (69.2%) patients experienced biological remission in the absence of pharmacological treatment. Mean time to remission was 36 months (median 24, range 6–98). The probability of endocrine remission in the absence of any pharmacological therapy was 59% at three years and 77.6% at 7 years, which remained stable up to 9 years (fig. 1). There was a dramatic decrease of pretherapeutic UFC after GKRS (fig. 2). Univariate analysis failed to find a predictor of biological remission, although age was close to statistical significance.

Figure 1: Probability of biological remission in the absence of pharmacological treatment after Gamma Knife radiosurgery; the number of patients for the time-points at 12, 24, 36, 51 and 96 months were 21, 15, 11, 7 and 3, respectively.



Biological remission in relation to BED by H-BED and L-BED

Higher BED was associated with a higher overall probability of biological remission (77% vs 66% at last follow-up), although this did not reach statistical significance (fig. 3). Of note, the number of patients reflecting such an actuarial probability at 12, 24, 36, 51 and 96 months were 21, 15, 11, 7 and 3, respectively.

Table 1: Demographic data.

Parameter	Value
Follow-up period (months), median (range)	80 (19–141)
Age at treatment (years), median (range)	39 (15.4–69.5)
Sex (M:F)	6:20
Symptoms at presentation	
– Cushing	20/26 (76.9%)
– Subjective visual symptoms	2/26 (7.7%)
– Pituitary insufficiency	4/26 (15.4%)
Initial treatment	
– Surgery	20/26 (76.9%)
– Pharmacological	6/26 (23.1%)
After failure of pharmacological treatment all had microsurgical resection	
Size at discovery	
– Macroadenoma	12/26 (46.1%)
– Microadenoma	14/26 (53.9%)
Surgical approach	
– Transrhinoseptal	17/26 (65.4%)
– Endonasal transsphenoidal	9/26 (34.6%)
Number of previous surgeries	
– Zero	0/26 (0%)
– One	21/26 (80.8%)
– Two	5/26 (19.2%)
Postoperative residual volume (cc), mean (median, range)	0.407 (0.097, 0.023–1.4)
Anatomical location of residual tumour	
– Cavernous sinus	11/26 (42.3%)
– Intrasellar	12/26 (46.2%)
– Intrasellar and cavernous sinus	3/26 (11.5%)
Side	
– Right	7/26 (26.9%)
– Left	19/26 (73.1%)
Reason for GKRS	
– Residual tumour and persistent hypersecretion	11/26 (42.3%)
– Recurrent tumour and persistent hypersecretion	11/26 (42.3%)
– Perioperative complications with need to stop resection	4/26 (15.4%)
ACTH value before GKRS (pg/ml), median (range)	132 (30–2209)
Free urinary cortisol before GKRS (µg/24h), median (range)	404 (12–264)
Serum cortisol at 8 a.m. (nmol/l), median (range)	126.5 (51–469)
Treatment for pituitary insufficiency before GKRS	11/26 (42.3%)
Pharmacological treatment stopped before GKRS	0/26 (0%)
Delay between microsurgery and GKRS, median (range)	84.6 (11–182.5)

ACTH = adrenocorticotrophic hormone; GKRS = Gamma Knife radiosurgery

Table 2: Dosimetric data

Parameter	Median (range)
Prescription dose (Gy)	27.5 (24–35)
Number of isocentres	3 (1–17)
Target volume (cc)	0.11 (0.09–3.7)
Conformity index	97.5% (86–100%)
Selectivity index	68.5% (22–87%)
Gradient index	2.77 (2.61–3.38)
Treatment time (minutes)	33 (10.3–128.7)
Volume of visual apparatus receiving >8 Gy (mm)	0 (0–11.1)
Maximum dose received by the optic apparatus (Gy)	1.1 (1–12.4)
Dose received by optic apparatus – first 10 mm^3 (Gy)	2.8 (0.4–7)
Maximum dose received by the pituitary stalk (Gy)	6.3 (2.7–24.4)
BED (pituitary adenoma)	228.1 (160–248)

BED = biological effective dose

The area under the ROC curve in general was 0.6 for the BED (continuous values) and 0.56 for the prescribed dose.

Figure 2: Urinary free cortisol levels before Gamma Knife radiosurgery (GKR) and at last follow-up after GKR.

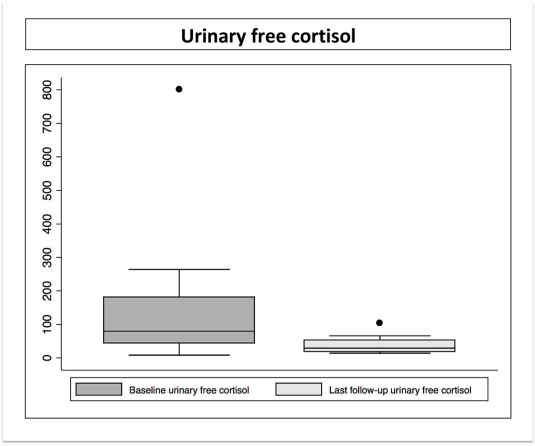


Figure 3: Probability of endocrine remission with high and low BED; the number of patients for the time-points at 12, 24, 36, 51 and 96 months were 21, 15, 11, 7 and 3, respectively. BED = biological effective dose in $Gy_{2.47}$

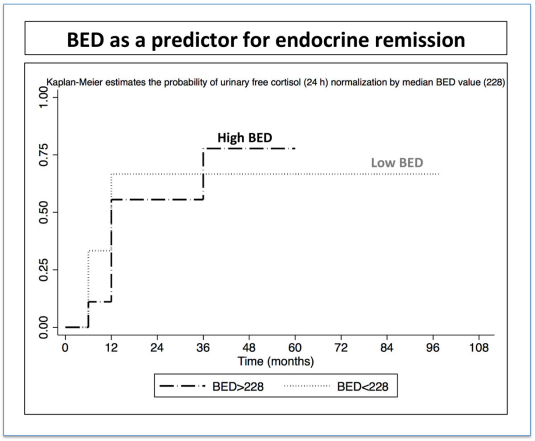


Table 3: Univariate analysis.

Variable	Odds ratio	Confidence interval	p-value
Univariate analysis, urinary cortisol normalisation			
Sex (M/F)	1.8	0.134–24.159	0.65
Age (continuous value)	1.055	0.952–1.168	0.3
Side	0.705	0.053–9.265	0.79
Serum cortisol at 8 a.m.	0.999	0.986–1.011	0.9
UFC (24 hours)	0.998	0.992–1.003	0.507
ACTH at baseline	1.103	0.953–1.275	0.18
Volume of residual tumour	1.0008	0.998–1.003	0.56
Dose	0.830	0.549–1.254	0.37
BED	0.996	0.945–1.050	0.901
Number of isocentres	1.152	0.820–1.617	0.41
Treatment time	1.003	0.964–1.044	0.84
Univariate analysis, biological normalisation and pharmacological treatment stop			
Sex	1.166	0.166–8.185	0.87
Age	0.985	0.927–1.046	0.62
Side	3.5	0.346–35.371	0.28
Serum cortisol at 8 a.m.	0.990	0.979–1.002	0.109
UFC (24 hours)	1.003	0.994–1.011	0.45
ACTH at baseline	1.003	0.995–1.010	0.38
Volume of residual tumour	0.999	0.998–1.0004	0.26
Dose	1.070	0.804–1.424	0.63
BED	1.014	0.978–1.051	0.44
Number of isocentres	1.062	0.885–1.274	0.51
Treatment time	0.988	0.963–1.015	0.41
Pituitary insufficiency			
Sex	1.222	0.196–7.594	0.32
Age	0.941	0.880–1.006	0.06
Side	0.545	0.094–3.145	0.49
Serum cortisol at 8 a.m.	1.0007	0.992–1.009	0.86
UFC (24 hours)	1.002	0.995–1.009	0.43
ACTH at baseline	1.0004	0.998–1.002	0.67
Volume of residual tumour	0.999	0.998–1.0008	0.76
Dose	1.102	0.844–1.438	0.47
Dose at stalk	1.032	0.916–1.163	0.59
BED at stalk	1.0006	0.989–1.012	0.9
Number of isocentres	1.036	0.884–1.213	0.66
Treatment time	1.018	0.990–1.047	0.19
ACTH = adrenocorticotrophic hormone; Bed = biological effective dose; UFC = urinary free cortisol			

Pituitary insufficiency after Gamma Knife radiosurgery

Seven patients developed new pituitary insufficiency after GKRS. The probability of this complication was 16% at 1 year and 32% at 3 years, which remained stable up to 9 years (fig. 4). The specific hormones related to pituitary insufficiency after SRS were ACTH in four cases, thyroid-stimulating hormone in two and follicle stimulating hormone / luteinising hormone in one.

Visual status changes

Two (7.7%) patients experienced transient visual acuity changes at 6 and 12 months after GKRS, respectively. Both completely recovered.

The prescribed marginal doses to the tumour was 24 Gy and 25 Gy, respectively. The BED values received by the tumour were 228.9 and 195.7, respectively. The maximum doses received by the optic apparatus were 9.4 and 9.3 Gy, respectively and the first 10 mm^3 of the optic apparatus received 7.4 and 7.3, Gy, respectively. The distance between the tumour and the optic apparatus was 3.6 mm in one case and 4 mm for the second case.

Other neurological complications

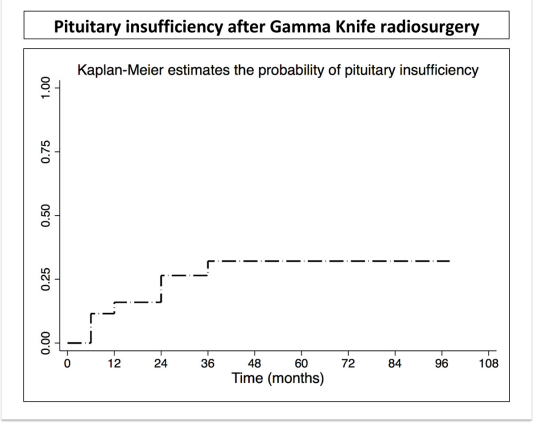
No other neurological complication was encountered.

Discussion

Summary of the present findings

In the present study, we report our experience with GKRS for Cushing disease. Eighteen (69.2%) patients experienced biological remission in the absence of pharmacological treatment. The probability of endocrine remission in the absence of any pharmacological therapy was 77.6% at 7 years, and remained stable up to 10 years. In this small series, higher BED (≤228 versus >228) was associated with a higher overall probability of biological remission (77% versus 66% at last follow-up), although this did not reach statistical significance. Of note, the numbers of patients reflecting such an actuarial probability at 12, 24, 36, 51 and 96 months were 21, 15, 11, 7 and 3, respectively. Moreover, the last three patients all belonged to the low BED group and were not distributed between the two groups (low and high BED), which can be further depicted in the Kaplan-Meier curve. The area under the ROC curve in general was 0.6 for BED continuous values and 0.56 for the prescribed dose. Seven patients developed new pituitary insufficiency after GKRS with a probability of this complication of 16% at 1 year and 32% at 3 years, subsequently remaining stable over time.

Figure 4: Probability of pituitary insufficiency after Gamma Knife radiosurgery.



Transsphenoidal surgery as the mainstream treatment for Cushing disease

Transsphenoidal surgery remains the mainstream treatment for Cushing disease [8, 12, 27, 28]. However, definitive surgical cure remains challenging because of early failures (persisting Cushing disease, usually considered within the first 6 months postoperatively) or late recurrences of the disease, more than 6 months after surgery [29, 30]. Incomplete microsurgical resection ranges from 20% to 80% [31–33]. Surgery may be precluded for older patients and those with extensive comorbidities. Persistent and untreated biological disease potentially has mortality rates as high as 50% [34].

The established role of GKRS for recurrent or persisting Cushing disease

During the past three decades, several studies have reported results with SRS for Cushing disease [14–17, 35–38]. Radiosurgery is typically an adjuvant management in patients with persistent Cushing disease. Classically, higher doses of irradiation are prescribed, as high as 30–35 Gy, in secretory pituitary adenomas [35]. The recent international multicentre study by Mehta et al. [15] included a large number of patients (n = 278) with a mean follow-up of 5.6 years. Mean marginal dose was 23.7 Gy. Cumulative initial control of hypercortisolism was 80% at 10 years and the mean time to cortisol normalisation was 14.5 months. Recurrence occurred in approximately 18% of cases [15]. The authors suggested that GKRS could result in shorter response times than conventional radiotherapy in this indication [15]. Other studies reported that Cushing disease cases achieved earlier and far better biological remission as compared with acromegaly after single-fraction GKRS [39].

New treatment paradigms in the context of GKRS for recurrent or persisting Cushing disease

Recently, several studies proposed new treatment paradigms in order to achieve better biological remission in Cushing disease. Hugues et al. [14] analysed cases with persistent or recurrent Cushing disease after prior transsphenoidal surgery. Two groups were reported, of whom one had GKRS alone, and the other underwent GKRS and bilateral adrenalectomy. The authors concluded that patients with mild to moderate Cushing disease could be safely managed with GKRS alone, whereas those with severe Cushing disease should be considered for bilateral adrenalectomy with either concurrent SRS or SRS performed at a later date if tumour growth occurred. We agree with the radiosurgical treatment algorithm for patients with persistent or recurrent Cushing disease after transsphenoidal surgery as presented by Hugues et al. [14]. Other studies suggested even that whole-sellar irradiation [40] provides high rates of endocrine remission as, and similar complications rates to, the classical series which describeed targeting only clearly visualised tumour [17, 38].

The most common complication in these series was hypopituitarism [17, 38].

In our present case series, we prescribed a high mean marginal dose of 28.5 Gy (median 27.5). This is probably a reason for not finding a statistically significant relationship between dose and endocrine remission in this small cohort. Moreover, we completely agree with a recent comment made by Dade Lunsford [14], that the necessary prescription dose remains unclear. The idea of prescribing higher radiation doses, as high as 50 Gy, as proposed by the Pittsburgh team, in a single fraction for small secreting tumours not close to the optic apparatus sounds appealing and remains to be elucidated by further studies.

Critical structures in the context of GKRS irradiation

An important aspect is the proximity of such residual tumours to two critical anatomical structures, namely the optic apparatus and the pituitary stalk. Due to the steep gradient of GKRS, a distance of only few millimetres is often sufficient to avoid visual complications, while delivering a therapeutic dose to the tumour. Recent papers suggested that the optic apparatus might receive doses up to 12 Gy without major risks for optic neuropathy [41].

An open question is whether hypofractionnated SRS could play a role in Cushing disease. The recent LGK ICON [42] nicely addresses such a point. While keeping the steep gradient of the LGK, it offers a high definition motion management control system. This could be particularly useful for patients with larger lesions, as well as for lesions in contact with or encasing the optic pathways. The safety and efficacy of this type of approach remain to be elucidated by further research.

The potential role of BED in single-fraction radiosurgery

In single-fraction radiosurgery, a certain physical dose is delivered within a given time period. The importance of these two variables (irradiation time and prescribed dose) can be further evaluated using the BED concept. This is particularly important as major variations in the irradiation time can appear for uniform prescribed doses or a narrow range of marginal dose prescription (such as in our study).

In 1989, the term BED was coined based on linear quadratic cell survival in radiobiology [43]. The main aim was to indicate quantitatively the biological effect of any radiotherapy treatment. In that context, BED took into account the changes in dose-per-fraction or dose rate, total dose and the time factor [43]. There utility of this parameter expanded in various fields, such as dose escalations or quantification of treatments using ionising radiation [43], among others.

The potential role of BED in single-fraction radiosurgery for Cushing disease

Recently and for the first time, BED has been suggested as a better predictor than the prescribed dose for safety and efficacy in single-fraction GKRS for trigeminal neuralgia by Tuleasca et al. [22]. Based upon this previously published research, we sought to evaluate the role of this parameter in the context of GKRS for Cushing disease for the first time, in this small cohort. After separation into two groups, our data suggest that higher BED was associated with better endocrine remission rates. Owing to the limited sample size, this aspect remains to be further demonstrated by other studies. The area under the ROC curve was higher for the BED than for the dose.

The potential role of BED as a predictor of safety and efficacy in other indications for single fraction GKRS

The present study is in continuity with a previous one from our group, which showed similar findings after single-fraction GKRS for acromegaly, suggesting a prominent role for higher BED values as related to better rates of endocrine remission [23]. Moreover and also recently, also using data from our institution, we showed that BED (as continuous values) is a stronger predictor for arteriovenous malformation obliteration after GKRS as compared with the marginal prescribed dose, in a cohort where the vast majority of patients (around 80%) were treated with a uniform dose of 24 Gy [24].In the future, BED might replace the marginal prescribed dose as a better predictor for safety and efficacy. Such findings should be replicated for other pathologies and in larger cohorts. We consider that, in the near future, radiosurgery will evolve towards tailored radiobiological effects, in which BED might play a key role. By analogy with dose de-escalation over the decades [44], the same might apply to BED during future decades, if such a concept demonstrates a prominent role and if the scientific community demonstrates its potential utility in the clinical realm.

Limitations

Our study has several limitations. One of the first major limitations is the retrospective data analysis, with all the biases that are involved in this type of methodology. A second is related to the limited number of cases, which precluded a multivariate analysis. This further applies to the BED evaluation, which included only a limited number of patients in one of the two arms (the higher BED arm). A third limitation, which is also related to the small subset of patients at each time-point, is that the Kaplan-Meier estimates can be misleading and should be interpreted with caution. A fourth limitation is the calculation of BED by means of a simplified formula, including only the beam-on time and the prescribed dose. A fifth limitation is related to the timeframe of our analysis, while we currently observe refinements of SRS platforms, including LGK, neuroimaging modalities. In this respect, even better results could potentially be obtained and reported in the near future. A sixth limitation is the fact that follow-up data came from various centres, and not only from the Lille University Hospital. Each of them might have different criteria for endocrine remission, normalisation of 24-hour UFC.

Conclusions

Using GKRS for Cushing disease, we report high endocrine remission rates, as high as 77.6% at 7 years, using high doses of radiation. Seven patients developed new pituitary insufficiency after GKRS, with a probability of developing this complication of 32% at 3 years, which further remained stable up to 9 years.

Our strategy was always to prescribe high doses of irradiation to the tumour in order to ensure high rates of endocrine remission, while paying close attention to the maximum doses received by the optic apparatus in order to avoid op-

tic neuropathies after GKRS. The appearance of pituitary insufficiency was considered in our centre as a secondary effect, which can be safely managed by substitution medication in the frame of a multidisciplinary management.

Our series is small, but raises the question of the impact of BED on biological remission after GKRS for Cushing disease. Higher BED values resulted in higher cure rates, although this did not reach statistical significance. Moreover, the area under the ROC curve was higher for the BED than for the prescribed dose. How BED should be incorporated into further dose planning remains to be established in the near future.

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No conflict of interest relevant to this article was reported.

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