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Gamma knife radiosurgery in patients with Cushing's Disease: Is it a curative option?

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Abstract

Background: The first line of treatment of Cushing's disease (CD) is surgery. However, surgical resection is not amenable in all cases and the role of radiosurgical management of residual tumors or upfront treatment has been reported. Our study highlights the effectiveness and safety of Gamma Knife Radiosurgery for the treatment of Cushing's disease.

Methods: This was an ambidirectional descriptive cohort study on 16 consecutive patients with a confirmed Cushing's disease that underwent Gamma Knife Radiosurgery (GKR) before July 2014 and assessed for outcome during the study period between January 2014 and June 2016 (30 Months). We included patients with a minimum of two years follow up. The main outcomes were biochemical remission and tumor volume control. Secondary outcomes were visual field changes and morbidity.

Results: Sixteen cases with CD were included into the study. The Mean age ± SD was 34.81 ± 10.10 years. The male to female sex ratio was 1:3.

Six cases (37.5%) were de novo. Normalization of hypersecretion at 2 years was achieved in 13 cases (81.3%).The median hormone normalization time was 23 months. Tumor volume control was achieved in all the cases, whereas tumor shrinkage was achieved in (10 cases) 62.5%. The median shrinkage time was 13 months. Of the 12 eyes with pre-Gamma Knife visual affection, 8 (75%) normalized, 4 (25%) improved, and none deteriorated. No patient developed new hypopituitarism after GK radiosurgery. One case developed diplopia at 24 months follow up from abducens palsy. No mortality occurred in our series.

Conclusion: Gamma Knife Stereotactic Radiosurgery is an effective and safe treatment option for Cushing's disease. It can be used as a complementary therapeutic procedure to classic surgery or as a first line treatment in selected number of patients.

Keywords: Adenomas, Cushing's disease, Outcome, Pituitary adenoma, Gamma Knife, Radiosurgery

Introduction

Corticotrophin adenoma of the anterior pituitary is responsible for the hypercortisolemic state Cushing's disease (CD). From the stand point of diagnosis and therapy, no pituitary tumors present a greater management challenge than corticotrophin adenomas [1]. Two entities worth mentioning are Cushing's syndrome and Cushing's disease. *Cushing's syndrome (CS)* results from prolonged exposure of tissues to excess of glucocorticoids and has been etiologically subdivided into *ACTH (Adrenocorticotropic Hormone)- independent (nonpituitary) or ACTH-dependent* [1].

CD is most often caused by solitary intrasellar microadenoma. Macroadenomas account for up to 10% of Corticotropinomas with invasiveness being more frequent at the younger age [2].

The diagnosis of Cushing's disease is challenging [3]. The 24-Hour Urinary Free Cortisol measurement (UFC)

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is the best screening test once Cushing's syndrome is suspected [4, 5]. Confirmation of CD is achieved by CRH stimulation test [4] and lateralization of the pituitary microadenoma is might be defined by a corticotrophin Inferior Petrosal Sinus gradient [6].

The first line of treatment of Cushing's disease is surgery, because there is no generally effective medical treatment to control corticotrophin hypersecretion [7]. Most ACTH-secreting pituitary tumors are microadenomas and as such the transsphenoidal route is appropriate and achieves a cure rate of 80–90% in skilled hands [8].

Surgical resection is not amenable in all cases, and the role of radiosurgical management of residual tumors or upfront treatment has been reported for functioning pituitary adenomas [9–12]. However, there is limited literature focusing on Cushing's disease due to difficulty in diagnosis and relative rarity of the disease [12–14]. Our study was aimed at assessing the effectiveness (biochemical remission and tumor volume control) and safety of Gamma Knife Radiosurgery for the treatment of Cushing's disease.

Patients and methods

This was an ambidirectional descriptive cohort study on 16 consecutive patients with a confirmed Cushing's disease that underwent Gamma Knife Radiosurgery (GKR). The patients were treated at Nasser Institute Gamma Knife Center in collaboration with the department of Neurosurgery Ain Shams University, Cairo, Egypt.

The study period was from January 2014 to June 2016, a duration of 30 months. Patients who had received GKR before July 2014 were reviewed for outcomes during the study period.

Patients enrolled were diagnosed in a coordinated four step diagnostic approach: Firstly, a general clinical evaluation; secondly, an establishment of an endocrinological diagnosis; thirdly, securing an anatomical diagnosis and finally assessment of the visual apparatus. We included patients with a minimum of two years follow up.

Excluded from the study were patients with Non-Functioning Pituitary Adenomas, functioning adenomas other than Cushing's disease, cases with a follow up duration of less than 24 months and patients refusing to join the study.

Radiosurgery technique

All Patients were treated with Gamma Knife Radiosurgery either adjuvant (post microsurgical resection) or upfront. Treatment was performed using the Leksell Gamma Unit Model C or Perfexion, Elekta Instruments, Stockholm. The radiosurgery treatment was delivered as an outpatient procedure using a technique previously described [15, 16] as follows:

A local anesthetic agent was applied to the patient's head followed by placement of the Leksell Stereotactic head frame (Model G, Elekta AB). High-resolution and thin slice (1.6 mm) gadolinium-enhanced MRI (Magnetic Resonance Imaging) was performed using a 1.5-T Genesis Sigma MR unit (General Electric). Magnetic Resonance Imaging was the only imaging technique used. Images were transported to the Gamma Plan 5.32 workstation (Elekta AB). Treatment planning included drawing of the target and delineation of the anterior visual pathway. Radiation coverage was generally intended to be $\geq$ 90% of the target; however, in some cases in which the tumor was in direct contact with the optic apparatus, coverage was intended to be at least 80%–85% of the tumor receiving the prescribed dose. The maximum dose directed at the optic apparatus was maintained below 9 Gy (Gray) when possible, without significant compromise of the tumor cover. Otherwise, in situations in which the maximum dose exceeded 9 Gy, a dose-volume histogram was created and the volume of anterior visual pathway receiving more than 9 Gy was kept lower than 10 mm^3.

The treatment planning was done using HP (Hewlett Packard) computer hardware and Unix software as an operating system. GammaPlan (Elekta Instruments Inc) version 5.32 (Model C) and Leksell GammaPlan version 10.0 (Perfexion) were the planning softwares used.

Outcome

The main outcomes were biochemical remission and tumor volume control. Secondary outcomes were visual field changes and morbidity.

Follow-up

Follow up was bi-annually for the first two years and annually for the rest of the years. Follow up included a clinical, radiological, biochemical and visual assessment.

Clinical follow up

Post-radiosurgery clinical features were reviewed and compared with pre-treatment manifestations.

Radiological follow up

A contrasted MRI sella was reviewed and pre- and post- treatment radiological characteristics compared, especially for any tumor volume changes. Tumor volume changes were evaluated in two ways: By using the micrometer screw gauge in the 3D planes (axial, coronal and sagittal). In addition, a qualitative assessment was done by registering the change in tumor contour or noting tumor retraction away from the normal tissue (e.g., from optic nerves or chiasm). Tumor volume

changes were categorized as: shrinkage, stable (stasis) or progression.

Tumor volume shrinkage was defined as a reduction in tumor size in at least two orthogonal planes by more than 20%. Tumor volume stability was defined as no change or change in less than two orthogonal planes. Tumor progression or enlargement was defined an increase in tumor size in at least two orthogonal planes by more than 20%. i.e., tumor growth within the planned treatment volume or adjacent to it was considered tumor progression. Tumor growth control was defined as either overall tumor shrinkage or stability at the last follow-up before time of data analysis comparing the last MRI with the pre-treatment one [17].

Biochemical follow up

Biochemical outcome was categorized into three: hormonal level normalization (or control), reduction or unchanged, with a plus one condition tagged as "pituitary deficiency."

Biochemical *Normalization* was defined as a hormonal level within or below the accepted normal reference range. *Hormonal reduction (improvement)* was defined as the decrease in hormonal levels by more than 50% but not reaching the normal reference range. Otherwise, the hormonal level was described to be *unchanged*. Pituitary deficiency was defined as a requirement for new hormonal replacement medication after SRS or a requirement for a dose increase in preexisting hormone therapy [17].

Visual field assessment

A computerized Visual field was ordered during each follow up visit. The perimetry findings were compared with respect to overall appearance and quantitative data registered on the forms. Visual outcome was tetrachotomized into: normal, improvement, stable or visual field reduction. Visual deficit due to SRS was regarded if the patient reported post-radiosurgery visual complaints related to damage to the perisellar optic apparatus confirmed by visual field and acuity examinations [17].

Statistical analysis

Data were presented as the median (p25, p75) or mean (± standard deviation (SD)) for continuous variables, and as the frequency and percentage for categorical variables.

Statistics of means were performed using the unpaired Student t-test both with and without equal variance (Levene's test) or ANOVA (Analysis of Variance) as necessary and the Wilcoxon rank-sum tests Or Kruskal Wallis test when variables were not normally distributed.

Statistical analyses of categorical variables were performed using the Chi square and Fisher exact test, as appropriate. Kaplan–Meier plots for endocrine remission and tumor volume control using the dates of the first SRS, and respective time to remission and shrinkage. Hormone remission and progression-free survival time were calculated from the day of the first SRS by using the Kaplan–Meier's method. Univariate analysis was performed on the Kaplan–Meier curves using log-rank statistics. Stratified analyses were done for variables to check for confounders.

A $p \leq 0.05$ was considered statistically significant. Commercially available statistical processing software (Stata,version 11.0, Stata Corp.) was used (Figs. 1, 2, 3, 4, 5).

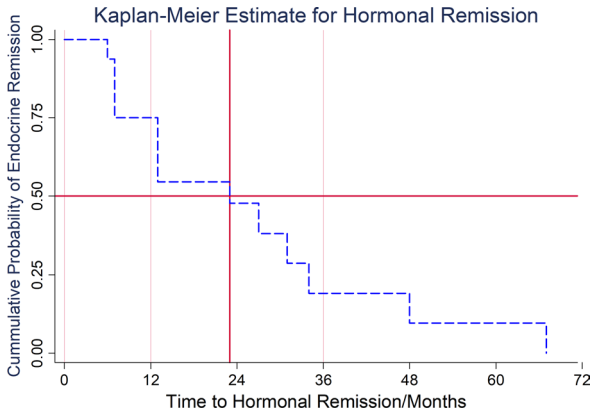

Fig. 1 Kaplan–Meier curve for hormone normalization

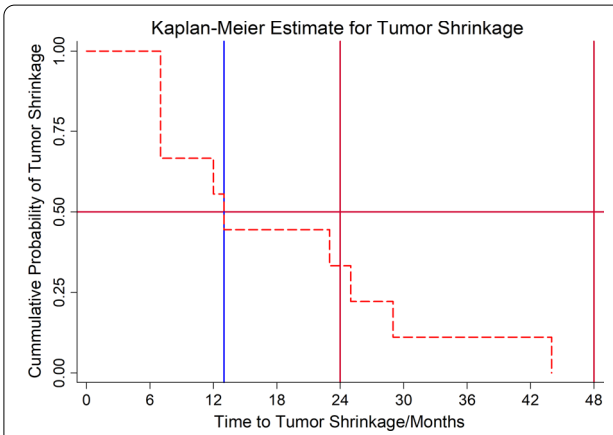

Fig. 2 Kaplan–Meier survival for tumor shrinkage

Results

Baseline sociodemographic data

Sixteen cases with Cushing's disease (CD) were included into the study. The Mean age ± Standard Deviation (SD) was 34.81 ± 10.10 years. The male to female sex ratio was 1:3.

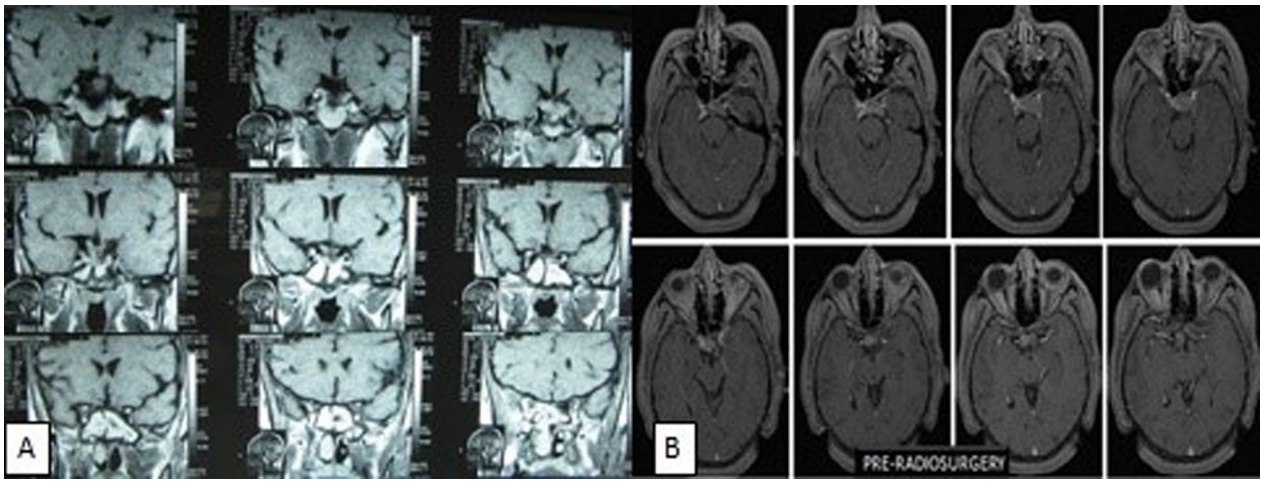

Fig. 3 Case N° 2: MRI brain (coronal (**A**) and axial cuts (**B**)): pre-GK radiosurgery

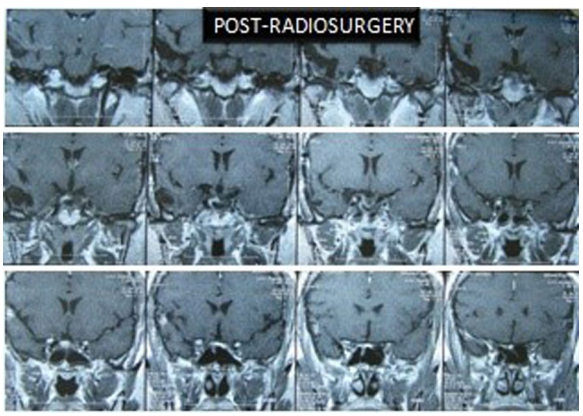

Fig. 4 Case N° 2: MRI brain (coronal cuts): post-GK radiosurgery

History of previous surgery

Six cases (37.5%) had no surgery label. Ten patients (62.50%) had undergone surgery as follows: single attempt surgery in 9 cases, and twice trails surgeries in one case. The median time between last surgery and Gamma Knife radiosurgery (GKR) was 34 months (p25 p75 20 40, and min.- max. 3 113 months).

Baseline clinical features

All the 16 patients (100%) with ACTH secreting pituitary adenoma had hormonal manifestations related to persistent elevated serum cortisol. None had headache as presenting symptom likewise none had ocular palsy. Hypertension was present in 12 (75%) cases and diabetes in 8 (50%). No patient had pretreatment pituitary insufficiency.

The median duration of Cushing's disease features was 2 year [(p25 = 1 p75 = 5) (Min. = 1 Max. = 8)].

Baseline visual affection

All the 16 patients had a pre-treatment visual field assessment. Visual affection was present in 8 patients (50%), was bilateral in 4 cases (50%) (Table 1).

Tumor operative status, location and associated findings

The tumor was located in the sella turcica in 13 cases (81.3%). The tumor was infiltrative in 4 patients (25%). One case had an associated cyst and one presented with apoplexy (Table 2).

Treatment of the patients

Number of treatments

The 16 patients received a cumulative 18 Gamma Knife treatments. In 14 patients (87.5%), the treatment was "single," while in 2 cases (12.5%) (all macroadenomas) it was two-staged. The average time between the staged treatments was 6 months. The median target volume was 1.4 cc (p25 = 0.44 p75 = 1.7) (min. = 0.26 max. = 9.6). In our sample, the mean (± standard deviation) maximum Dose to the Visual Pathway was 7.8 ± 1.1 Gy with a range of 4.4 to 10 Gy. The average Brainstem volume receiving ≥ 12 Gy was 81.7 ± 73 mm^3 (min = 1.3 Max. = 350). The treatment parameters (coverage and doses) are presented in Table 3.

The mean follow-up duration (time from first Gamma Knife treatment to last follow up visit) was 46.3 ± 21.7 months and ranged from 24 to 110 months.

Indication for GKS

Gamma knife radiosurgery was the second line of treatment in 10 patients (62.5%) with Cushing's disease. Of the 6 patients with de novo lesion two had received ketoconazole

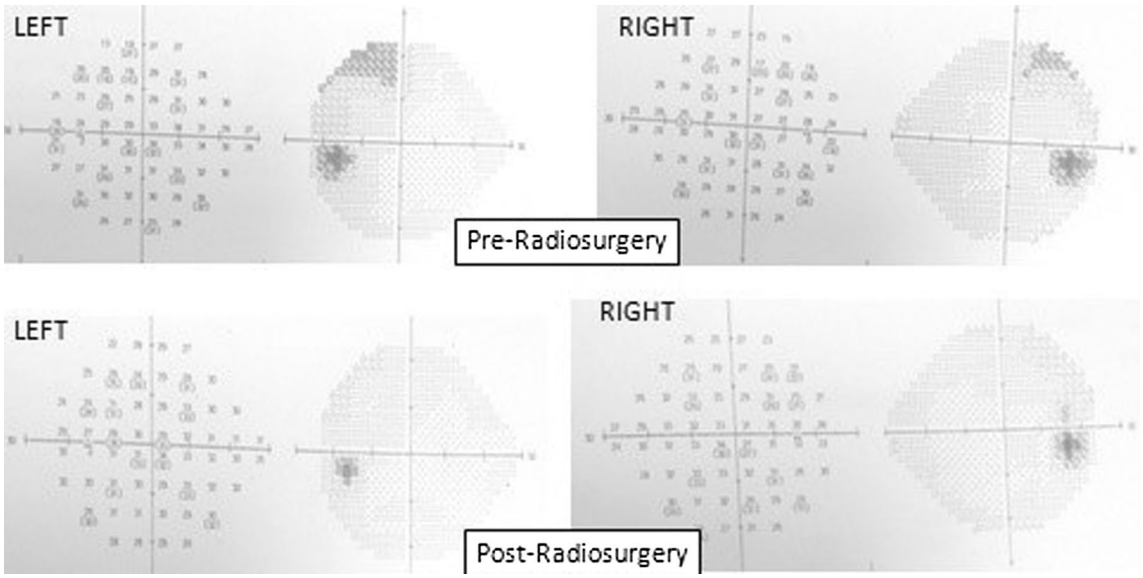

Fig. 5 Case N° 2: visual field (pre- and post-radiosurgery)

Table 1 Baseline clinical characteristics of the patients

	Cushing's disease ***N*** **= 16**
Hypertension	
Yes	12 (75)
Diabetes mellitus	
Yes	8 (50)
Headache	
Yes	0 (0)
Hormonal manifestations	
Yes	16 (100)
Visual affection *n* = 16	
Yes	8 (50)
Laterality of visual affection *n* = 8	
Unilateral	4 (50%)
Bilateral	4 (50%)

Table 2 Tumor Location and Associated findings

Parameter	**Number (%)**
Tumor status	
Denovo	6 (37.50)
Residual	10 (62.5)
Tumor site	
Sellar	13 (81.3)
Suprasellar	3 (18.8)
Parasellar	1 (6.3)
Infrasellar	1 (6.3)
Infiltrative	
Yes	4 (25)
Associated cyst	
Yes	1 (6.3)
Apoplexy	
Yes	1 (6.3)

with no effect on hormone level. The six refused microsurgery and opted for Gamma Knife radiosurgery.

Outcome after GK radiosurgery

The main outcomes of Gamma Knife Surgery were patients' hormonal changes and tumor volume changes. Secondary outcomes were visual field changes and morbidity.

Outcome: biochemical remission

Normalization of hypersecretion was achieved in 13 cases (81.3%).The median hormone normalization time

Table 3 Treatment parameters

Parameter	**Mean ± SD (Min Max)**
Percentage cover	93 ± 7.6 (75 100)
Prescription isodose/Gy	57.9 ± 12.8 (50 90)
Prescription dose/Gy	27.6 ± 4.2 (18 35)
Minimum dose/Gy	16.3 ± 8 (2.2 30.6)
Maximum dose/Gy	48 ± 12 (27.8 70.1)
Mean prescription dose	37 ± 9 (23.1 56.4)
Integral dose/mJ	61.7 ± 52.3 (9.1 221.4)
Maximum dose to the visual pathway/Gy	8 ± 1.4 (5.2 10)

(time taken for 50% of the cases to remit) was 23 months. Hormonal remission at 36, 48 and 60 months follow-up was, respectively, was 80%, 82% and 90.5% (Table 4).

Factors affecting hormonal changes

Since hormone control (normalization and improvement) was achieved in almost all patients, we will subsequently focus on the factors that affected "hormone normalization only."

Pre-radiosurgery hormonal levels

Patients that achieved biochemical remission had a lower pre-radiosurgery hormone level (Table 5). There was no statistically significant association between pre-radiosurgery hormone levels and hormone normalization ($p=0.3819$).

Age

There was no statistically significant difference in the mean age in patients with and without hormonal normalization ($p=0.89$).

Table 4 Tumor volume and biochemical control

Outcome	Cushing $N=16$
Follow up duration	
Mean ± SD	46.3 ± 21.7
(Min. Max.)	(24 110)
Hormonal changes	N (%)
Normal	13 (81.3)
Improved	1 (6.2)
Unchanged	2 (12.5)
Worse	–
Biochemical resolution	*N* (%)
Yes	13 (81.3)
No	3 (18.7)
Hormone remission time/months	
Median time (95%CI)	23 (7 31)
Tumor volume changes	*N* (%)
Disappeared	–
Shrinkage	10 (62.5)
Stable	6 (37.5)
Growth	–
Tumor control	*N* (%)
Yes	16 (100)
No	-
Tumor shrinkage	*N* (%)
Yes	10 (62.5)
No	6 (37.5)
Tumor shrinkage time/months	
Median time (95% CI)	13 (7 29)

Table 5 Pre- and post-radiosurgery 24 UFC hormonal levels

Statistics	24 UFC (μg/ day)	
	PreGK	PostGK
p25	391.1	52.3
p50 = Median	663	120.1
p75	1236.65	184.75
Min	182	8.3
Max	4108.8	558

Sex

Higher Hormonal resolution was achieved more in males (79.6%) than in females (73.8%) but the difference was statistically non-significant ($p=0.5$).

Tumor size

The median target volume for patients with lesions that completed resolution was 2.1 cc, while that for those without hormonal remission was 3.1 cc but the difference was not statistically significant ($p=0.14$). Tumors less than 2 cc had better hormonal remission (85%) compared to tumors greater than 2 cc. However, the difference was statistically significant ($p=0.04$).

Time interval between last surgery and Gamma Knife treatment

Patients treated within 6 months after last surgical operation had better hormonal resolution than those treated thereafter (< 6 months: 93% and > 6 months: 69%). These differences were however not statistically significant.

Prescription dose

Patients with tumors that remitted received a higher prescription dose (≥ 25.2 Gy) compared to those that did not have biochemical remission (mean prescription dose = 24.3 Gy) even though the difference was not statistically significant ($p=0.4$).

Tumor coverage

Patients with tumors having biochemical remission had a higher tumor coverage than those without hormonal resolution (90.4% versus 88.5% respectively). Higher tumor coverage (> 90%) was associated with a higher proportion of hormone normalization. The difference was however not statistically significant.

Outcome: tumor volume changes

Tumor volume control was achieved in all the cases, whereas tumor shrinkage was achieved in (10 cases) 62.5% of ACTH-omas. The median shrinkage time (time taken for 50% of the cases to shrink) was 13 months.

Age and sex

There was no statistically significant difference in tumor shrinkage in both males and females ($p = 0.91$). There was no statistically significant difference in the age at which the tumor shrunk ($p = 0.87$).

Tumor size

Lesions with tumor volume greater than 2 cc had a higher proportion of tumor shrinkage (83%) compared to lesions with tumor volume ≤ 2 cc (74%) although the difference was not statistically significant (p = 0.28).

Time interval between the last surgery and Gamma Knife radiosurgery

Patients who presented between 6 and 12 months had better tumor volume control compared to those who were treated within 6 months or one year after surgery. However, the difference was statistically non-significant ($p = 0.36$).

Prescription dose

For prescription doses of 10–35 Grays used in our study, there was no statistically significant association with tumor volume control ($p > 0.05$).

Mean dose, integral dose, minimum and maximum prescription doses

The average of the mean dose, integral dose as well as the minimum and maximum prescription doses did not differ statistically in patients that had shrunken or non-shrunken lesions ($p > 0.05\%$).

Biochemical control and tumor shrinkage

Tumors in Patients with hormonal control shrunk (81.6%) more than tumors in patients without biochemical remission (71%), although this was statistically non-significant ($p = 0.203$).

Visual outcome

Of the 12 eyes with pre-Gamma Knife visual affection, 8 (75%) normalized, 4 (25%) improved, and none deteriorated.

Morbidity and mortality

No patient developed new hypopituitarism after GK radiosurgery. There was no case of adverse radiation effect. No cases of recognized visual field -nor acuity-deterioration except for one case of 32-year-old female with a residual ACTH secreting adenoma with a pure sellar location who received a two-stage GK treatment and presented with diplopia at 24 months follow up from abducens palsy. Target volume was 3.1 cc, and percentage cover was 93%. However, the dose to visual apparatus was 7.4 Gy.

No mortality occurred in our study.

Illustrated case

Summary of history

The 39-year-old patient was diagnosed with Cushing's disease in the course of an investigation for secondary amenorrhea of 7 years duration. She was operated via the Transphenoidal approach with an uneventful post-operative period. Pre-radiosurgery MRI shows a residual tumor touching the optic chiasm, 24 h UFC in was 708 µg/day (*N* 28.5–213) and Visual field examination showed moderate upper bitemporal hemianopia. She was accepted for Gamma Knife treatment. She had secondary hypertension and diabetes mellitus.

Treatment

The 3.4 cc tumor was treated with 25 Gy to the 50% isodose with 79% cover. The maximum dose to the visual pathway was 8.4 Gy and only 200 cubic mm of the brainstem received ≥ 12 Gy which should be safe. The time interval between the Transphenoidal surgery and radiosurgery was 14 months.

Follow up and outcome

At the last (7 years) follow up: The tumor had shrunk (from 12 months), 24 h UFC levels were Normal (24 µg/day) (normalized at 6 months follow up) as well as the visual fields (normalized at 12 months). The Hypertension and diabetes mellitus had also normalized (since the 12 months follow up). There were no complications.

Discussion

The relative novelty of SRS in comparison to conventional radiotherapy warrants the conduction of studies to evaluate its effectiveness and complications in different settings. Previous study by Hafez RF et al., revealed encouraging results in terms of tumor volume control and biochemical remission but was limited in sample size as regard the biochemical variant and follow up duration (median 28 months) [18]. El Shehaby et al. published the results of Gamma Knife Radiosurgery on non-functioning pituitary adenomas [15]. Our study focuses on Cushing disease.

A minimum follow-up duration of 24 months was chosen since previous studies such the reviews by Sheehan et al. [19]., and most recently, Kim et al. [20] have revealed that this is the average minimum to achieve biochemical control.

Successful management of patients with Cushing's disease aims at achieving biochemical remission, preservation of normal pituitary hormonal production, improvement or maintenance of visual function, and tumor control [21, 22]. The main goal of stereotactic radiosurgery for Cushing's disease is biochemical control since hormone hypersecretion accounts for most of the clinical manifestations, morbidity and mortality. However, the effectiveness of SRS for the treatment of Cushing's disease is debated largely because of inconsistent methods of analysis and endocrine criteria of studies over the past decades [20–22]. Moreover, the criteria defining "remission" and "cure" have evolved and become more stringent over time [21, 22]. Most published literature accepts hormone remission to be defined as the basic hormone level within or below the accepted normal reference range with the patient off any hormone suppressive medications [17]. ACTH-omas are variable and difficult to interpret biochemical control given the lack of standardized criteria for post-radiosurgery hormonal control (e.g., 24-h Urine Free Cortisol versus serum ACTH versus basal serum cortisol) [13]. In our study, the *therapeutic evaluation criteria* was 24-h urine free cortisol for the assessment of hormonal control (according to the reference level for the laboratory). This is acceptable in published literature [20, 21, 23, 24].

In a recent systematic review based on 20 studies involving 580 patients with Cushing's disease**,** Kim W et al. reported complete endocrine normalization in 10–87% of patients with Cushing's disease [20]. In our study, biochemical remission was achieved in 13 cases (81.3%) which is within the range reported in most literature [20].

In one of the largest published series involving 90 evaluable cases of Cushing's disease that underwent SRS with a mean dose of 23 Gy (median 25 Gy) and mean endocrine follow up of 45 months, the normalization rate (24-h UFC) was 54% [13]. There was no apparent justification for this lower remission rate compared to our series. However, this could be attributed to the use of older techniques of treatment in the study since patients were treated in the 90 s, whereas their average time to remission was 13 months (range 2–67 months), endocrine relapse was seen in 20% of the patients between 6 and 60 months after GK SRS [13]. The latter suggests that despite evidence of hormonal remission after SRS, patients with Cushing's disease require life-long follow up to monitor for biochemical relapse.

For Cushing's disease like other functioning adenomas, microadenomas are associated with better response rate than macroadenomas [25] and remission rates may be improved by continuing medical therapy in the postoperative period [13].

MRI-defined local tumor control was used for tumor volume assessment. These criteria are consistent with current literature on SRS for FPA [11, 19, 20, 24]. In our study, tumor volume control was achieved in all the cases, whereas tumor shrinkage was achieved in 62.5% (10 cases) of ACTH-omas. Kim et al. [20] in a review based on 20 studies involving 580 patients with Cushing's disease, tumor control was achieved in 80–100% of patients, with decreased adenoma volume in 10–70% of patients. Microadenomas shrunk more than macroadenomas although the difference was not statistically significant. This finding was consistent with current literature [21, 26]. Yang I et al. explained that, with larger tumors, there is a tendency for greater extension into critical structures, such as the cavernous sinus and optic chiasm, limiting the efficacy of SRS by prohibiting the margin doses used around these structures [26]. In our study, the mean prescription dose to macroadenomas was 24.4 ± 5.4 Gy, while that to microadenomas was 28 ± 7.2 Gy, and the difference was highly statistically significant ($p = 0.005$).

No mortality occurred in our study. Mortality related to Gamma Knife radiosurgery has not been reported in the literature. Systematic reviews by Sheehan et al., Yang et al. and Kim W et al. did not reveal any deaths [19, 20, 26]. This further supports the safety of the technique.

Study limitation: In contrary of most studies on functioning pituitary adenomas, ours was limited by the relatively short follow up duration. The strength of our study is that it was confined to ACTH secreting adenoma.

Conclusion

Gamma Knife Stereotactic Radiosurgery is an effective and safe treatment option for Cushing's disease. It can be used as a complementary therapeutic procedure to classic surgery or as a first line treatment in selected number of patients.

Abbreviations

ACTH: Adrenocorticotropic hormone; ANOVA: Analysis of variance; FPA: Functioning pituitary adenoma; CD: Cushing's disease; CS: Cushing's syndrome; CRH: Corticotropin-releasing hormone; GK: Gamma Knife; GKR: Gamma Knife Radiosurgery; Gy: Gray; MRI: Magnetic resonance imaging; SD: Standard deviation; SRS: Stereotactic radiosurgery; UFC: Urinary free cortisol; 3D: Three dimensional; ACTH-oma: Adrenocorticotropin Hormone Secreting Adenoma; CS: Cavernous Sinus; CSF: Cerebro spinal fluid; CT: Computerized tomography; D2: Dopamine 2; DA: Dopamine Agonist; ENT: Ear nose and throat; FSH: Follicle stimulating hormone; GH-oma: Groth hormone secreting adenoma; GH: Growth hormone; GnRH: Gonadotropin releasing hormone; GHRH: Growth hormone releasing hormone; HE: Hematoxylin–Eosin; ICA: Internal carotid artery; IGF-1: Insulin growth factor 1; IPSS: Inferior petrosal sinus sampling; IRMA: Immunoradiometric assay; LH: Luteinizing hormone; MEN: Multiple endocrine neoplasia; NFA: Clinically nonfunctioning adenoma; OGTT: Oral glucose tolerance test; PRL: Prolactin; PRL-oma: Prolactin secreting adenoma; T4: Free thyroxin; TRH: Thyrotropin releasing hormone; TSH: Thyroid stimulating hormone; UFC: Urine free cortisol; VEP: Visual evoked potentials; WHO: World Health Organization.

Authors' contributions
TE contributed to Concept, Revision and Approval. INE contributed to Concept, Data collection, Statistical Analysis, Formatting, Revision. HR revision of manuscript, editing manuscript according to reviewers comments. AME revision of manuscript, editing manuscript according to reviewers comments. All authors read and approved the final manuscript.

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Availability of data and materials
The data that support the findings of this study are available from Cairo Gamma Knife Center (Nasser institute) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Cairo Gamma Knife Center (Nasser institute).

Declarations

Ethics approval and consent to participate
All procedures performed in studies involving human participants were in accordance with the ethical standards of the Research Ethics Committee of the Faculty of Medicine, Ain Shams University, Reference Number: 1832/2014 of 2/4/2014. All participants provided informed written consent to participate in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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