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Long-term Outcomes of Hypopituitarism following Gamma Knife Radiosurgery for Pituitary Adenomas

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Abstract

Background: Gamma knife radiosurgery [GKRS] is an established treatment for pituitary adenomas [PAs], particularly for recurrent or residual tumors following surgical resection. However, hypopituitarism remains a significant complication. This study evaluated the long-term outcomes of hypopituitarism following GKRS for PAs.

Patients and methods: This prospective study included 137 adult patients who underwent GKRS for PAs. Comprehensive endocrine evaluations were performed before and after treatment, including measurement of thyroid, adrenal, gonadal, and growth hormone function. Tumor volumes were calculated using standardized magnetic resonance imaging protocols, and tumor response was categorized as progression, shrinkage, or stable based on volumetric changes.

Results: Post-GKRS, significant reductions were observed in thyroid-stimulating hormone, cortisol, prolactin, growth hormone, and insulin-like growth factor-1 levels [p<0.001], while free triiodothyronine and thyroxine levels increased significantly [p<0.001]. Hypothyroidism was diagnosed in 58.39% of patient's post-treatment compared to 73.72% pre-treatment. New-onset hypopituitarism occurred in 13.14% of patient's post-treatment, significantly lower than the pretreatment rate of 36.5% [p<0.001]. Tumor progression occurred in 8.03% of cases. Larger tumor volume [OR=1.42, 95%CI:1.154-1.74] and tumor progression [OR=0.210, 95%CI:0.093-0.473] were independent predictors of hypothyroidism.

Conclusion: GKRS effectively controls PAs but carries a significant risk of endocrine dysfunction. Tumor volume and progression are independent predictors of post-GKRS hypothyroidism, emphasizing the need for long-term endocrine monitoring in these patients. Additionally, new-onset hypopituitarism significantly decreased post-GKRS, underscoring the importance of comprehensive pituitary function assessment following treatment.

Keywords: Gamma Knife Radiosurgery; Pituitary Adenoma; Hypopituitarism; Hypothyroidism; Tumor Volume.

INTRODUCTION

Pituitary adenomas [PAs] represent a significant proportion of intracranial neoplasms, constituting approximately 10-20% of all diagnosed brain tumors [1].

PAs are categorized according to their hormonal secretory activity into two primary groups: functioning PAs [FPAs], which produce biologically active hormones, and non-functioning PAs [NFPAs], which lack hormonal secretion [2].

The management of PAs typically follows established treatment paradigms. For most NFPAs and FPAs [with the exception of prolactinomas], surgical resection remains the primary therapeutic approach [3].

Despite the effectiveness of surgical intervention, its long-term efficacy is limited by significant recurrence rates, with approximately 20% of patients experiencing tumor recurrence following gross-total resection for NFPAs [4,5].

Given these limitations, radiosurgery has emerged as a critical treatment modality for specific patient populations. Gamma knife radiosurgery [GKRS] is indicated for patients with incomplete tumor resection, recurrent disease, persistent hormonal hypersecretion, or those with comorbidities that preclude surgical intervention [6].

For selected NFPA patients with documented growth of small tumors, cavernous sinus invasion, advanced age, or significant comorbidities, initial GKRS may serve as an alternative primary treatment [7].

Furthermore, GKRS has proven effective for dopamine agonist-resistant or intolerant prolactinomas, with reported hormonal remission rates varying between 4.5% and 83% [8]. The technique's capacity for highly precise, conformal, and focused radiation delivery has established GKRS as the predominant radiation approach for PAs [9].

Despite its efficacy, GKRS is associated with complications, with hypopituitarism being among the most common [10]. The temporal presentation of hypopituitarism typically occurs within 2-4 years' post-treatment [11], though the long-term risk increases substantially, potentially affecting up to 80% of patients. Notably, studies reporting the highest incidence of new-onset hypopituitarism tend to have the longest follow-up periods [12], highlighting the importance of extended surveillance. Currently, comprehensive long-term studies examining radiosurgery-related complications remain limited.

This investigation seeks to evaluate the long-term outcomes of hypopituitarism following GKRS for PAs.

PATIENTS AND METHODS

A prospective single arm study was conducted on 137 PA patients who were submitted for GKRS treatment at the Neurosurgery Department at Al-Azhar University Hospital, Egypt. The study was approved by the institutional ethical committee of our institution. Written informed consent was obtained from all participants prior to participation.

Patients were excluded from the analysis if they had inadequate endocrine follow-up [defined as less than 12 months of monitoring], previous radiation therapy exposure, pre-existing pituitary insufficiency prior to GKRS intervention, or absence of visible pituitary glands on imaging.

A comprehensive evaluation was performed for each patient, including a detailed medical and surgical history. Complete clinical examinations were conducted to establish baseline measurements and identify any pre-existing conditions that might influence treatment outcomes or interpretation of results.

Gamma knife radiosurgery [GKRS] technique:

For all radiosurgical interventions, the Leksell Gamma Knife Model B apparatus was utilized, with the stereotactic Leksell frame affixed under local anesthesia; subsequently, high-resolution, contrast-enhanced magnetic resonance imaging [MRI] scans, thinly sliced and focused on the sellar area, were obtained, while a collaborative team comprising a neurosurgeon, radiation oncologist, and medical physicist jointly formulated the Gamma Knife radiosurgery [GKRS] treatment strategy, administering a single-fraction GKRS session to each participant, wherein the radiation dosage was established based on an array of considerations such as tumor classification, size, nearness to the optic nerve and chiasm, and prior radiotherapy exposure, employing predominantly small [4 mm and 8 mm] collimators to ensure maximum precision and conformality.

Endocrine assessment:

Comprehensive endocrine evaluations were performed both before and after GKRS intervention. The assessment included measurement of multiple serum hormone levels to determine pituitary function across various axes. The specific hormones measured included:

Free triiodothyronine [FT3], free thyroxine [FT4], and thyroid-stimulating hormone [TSH] were assessed to evaluate thyroid function. Hypothyroidism was diagnosed based on low FT4 levels in combination with low, normal, or slightly elevated TSH levels.

Adrenal function was evaluated through measurement of cortisol and adrenocorticotropic hormone levels. Hypercortisolism was identified by morning [08:00] cortisol levels below 4 µg/dL or insufficient cortisol response [less than 20 µg/dL] during stimulation or insulin tolerance testing.

Gonadal function was assessed through measurement of follicle-stimulating hormone [FSH], luteinizing hormone [LH], testosterone [in men], and estradiol [in women]. In male patients, hypogonadism was indicated by low serum testosterone without concurrent elevation of LH and FSH. In female patients, hypogonadism was characterized by amenorrhea with low serum estradiol and low gonadotropin levels in premenopausal women, while menopausal women exhibited non-elevated gonadotropin [LH and FSH] levels [13].

The functionality of growth hormone [GH] was assessed by quantifying the concentrations of GH and insulin-like growth factor-1 [IGF-1], with GH deficiency identified through an inadequate response to insulin tolerance testing [below 5 µg/L] or diminished IGF-1 levels adjusted according to age and gender; additionally, prolactin concentrations were evaluated within a thorough endocrine analysis, and new-onset hypopituitarism post-GKRS was characterized as a recently observed deficit in any hormonal axis or the initiation of hormone replacement therapy required subsequent to the radiosurgical procedure, which had not been evident prior to intervention.

Imaging protocol and tumor assessment: Standardized MRI protocols for pituitary imaging were implemented for all patients before and after GKRS treatment. Tumor dimensions were meticulously measured in three perpendicular planes: transverse [TR], anteroposterior [AP], and craniocaudal [CC]. Tumor volumes were calculated using the formula: $V = [\pi \times [TR \times AP \times CC]]/6$[14]. The response of tumors to therapy was delineated based on volumetric alterations, wherein tumor progression was identified by an augmentation in volume of 20% or greater or any signs of renewed growth, while tumor reduction was marked by a decrease in volume of at least 20% absent any regrowth indicators; tumors exhibiting volumetric fluctuations within 20% of initial measurements were deemed stable, and parasellar invasion was categorized using the Knosp classification, with grades 3 or 4 signifying substantial encroachment, whereas suprasellar extension was described as the tumor's proximity within 2 mm of the optic nerve and chiasm, highlighting a crucial anatomical interaction potentially affecting therapeutic strategies and results.

Sample size calculation:

The sample size calculation was conducted using the Epi-Info 2002 statistical software package, which was developed by the World Health Organization and the Centers for Disease Control and Prevention. The sample size was determined based on a 95% confidence level, with the prevalence of new-onset hypopituitarism after five years estimated at 20%, as reported in a previous study [1], and a confidence limit of 7%. Consequently, 137 cases were required for recruitment.

Statistical analysis

Employing SPSS version 26 [IBM$^{Inc.}$, Chicago, IL, USA], the investigation scrutinized data through distributional normality assessment [Shapiro-Wilks and histogram], comparative analysis of parametric quantitative values [mean ± SD] via paired T-tests, and evaluation of categorical data [frequencies and percentages] using Chi-square tests, where a two-tailed P-value below 0.05 was considered statistically significant.

RESULTS

The mean age of the patients was 50.7 ±15.99 years. According to the gender distribution, males represent 41.61% and females represent 58.39%. The median value [IQR] of tumor volume at GKRS was 3.51 [1.71-5.38] cm^3. Tumor type was NFPAs in 83 [60.58%] patients, prolactinoma in 30 [21.9%] patients, acromegaly in 23 [16.79%] patients, and Cushing disease in 1 [0.73%] patient [Table 1].

GKRS was once in 116 [84.67%] patients, twice in 19 [13.87%] patients, three times in 2 [1.46%] patients. Progression of tumor occurred in 11 [8.03%] patients and shrinkage and stable of tumor occurred in 126 [91.97%] patients. The mean value [± SD] of tumor margin radiation dose was 15.8 [±4.6] Gy. The mean value [± SD] of maximum radiation dose was 38.9 [±12.02] Gy. The mean value [± SD] of prescription isodose was 40.7 [±7.96] % [Table 2]. Hypothyroidism and new-onset hypopituitarism after GKRS were significantly lower posttreatment than pretreatment [P<0.05]. FT3 and FT4 were significantly higher in posttreatment than pretreatment [P<0.001]. TSH, cortisol, prolactin, growth hormone, insulin-like growth factor-1 were significantly higher in posttreatment than pretreatment [P<0.001]. FSH, LH, testosterone, and estradiol were insignificantly different between pretreatment and posttreatment [Table 3].

Tumor volume at GKRS was significantly higher in hypothyroidism than No hypothyroidism [P<0.001] [Table 4]. Tumor progression and Tumor volume at GKRS were independent predictors of hypothyroidism [P value <0.001] while age, sex, tumor type and tumor margin radiation dose were not [Table 5].

Table [1]: Demographic data, tumor volume, and tumor type of the studied patients

		[n=137]
Age [years]		50.7 ± 15.99
Sex	**Male**	57 [41.61%]
	Female	80 [58.39%]
Tumor volume at GKRS [cm^3]		3.51 [1.71 - 5.38]
Tumor type	**Nonfunctioning adenomas**	83 [60.58%]
	Prolactinoma	30 [21.9%]
	Acromegaly	23 [16.79%]
	Cushing disease	1 [0.73%]

Data are presented as mean ± SD, frequency [%] or median [IQR]. GKRS: Gamma knife radiosurgery.

Table [2]: Tumor response and gamma knife radiosurgery parameters of the studied patients

		[n=137]
GKRS	**Once**	116 [84.67%]
	Twice	19 [13.87%]
	Three times	2 [1.46%]
Tumor response	**Progression**	11 [8.03%]
	Shrinkage and stable	126 [91.97%]
Tumor margin radiation dose [Gy]		15.8 ± 4.6
Maximum radiation dose [Gy]		38.9 ± 12.02
Prescription isodose [%]		40.7 ± 7.96

Data are presented as mean ± SD or frequency [%]. GKRS: Gamma knife radiosurgery.

Table [3]: Endocrine evaluations of the studied patients

	Pretreatment	Posttreatment	P value
Hypothyroidism	101 [73.72%]	80 [58.39%]	0.007
New-onset hypopituitarism after GKRS	50 [36.5%]	18 [13.14%]	<0.001
Free triiodothyronine [pg/mL]	2.3 ± 0.76	2.8 ± 0.52	<0.001
Free thyroxine [ng/dL]	2.3 ± 0.76	2.59 ± 0.96	<0.001
Thyroid-stimulating hormone [mU/L]	7.3 ± 1.94	3.54 ± 1.77	<0.001
Cortisol [nmol/L]	522.5 ± 215.63	492.51 ± 216.18	<0.001
Prolactin [ng/mL]	23 ± 8.44	18.55 ± 8.51	<0.001
Growth hormone [ng/mL]	11.5 ± 2.56	8.41 ± 2.6	<0.001
Insulin-like growth factor-1 [ng/mL]	199.4 ± 68.86	182.75 ± 69.69	<0.001
Follicle-stimulating hormone [mIU/mL]	10 ± 5.19	9.95 ± 5.19	0.180
Luteinizing hormone [IU/L]	6.2 ± 3	6.21 ± 2.99	0.104
Testosterone [ng/dL]	288.9 ± 322.93	288.91 ± 322.94	0.158
Estradiol [pg/mL]	57.1 ± 36	56.96 ± 35.94	0.095

Data are presented as mean ± SD.

Table [4]: Comparison of tumor volume between the two groups

	Hypothyroidism	No hypothyroidism	P value
Tumor volume at GKRS [cm^3]	4.2 ± 2.57	2.5 ± 1.99	**<0.001**

Data are presented as mean ± SD. GKRS: Gamma knife radiosurgery.

Table [5]: Univariate regression of risk factors versus hypothyroidism

	Univariate		
	Odds ratio	**95% CI**	**P value**
Age	0.988	0.964- 1.01	0.342
Sex	1.58	0.738- 3.42	0.235
Tumor type	1.017	0.495 - 2.47	0.803
Tumor progression	0.210	0.093-0.473	<0.001
Tumor volume at GKRS [cm^3]	1.42	1.154 -1.74	<0.001
Tumor margin radiation dose [Gy]	1.004	0.924 -1.091	0.908

CI: Confidence interval. GKRS: Gamma knife radiosurgery.

DISCUSSION

Hypopituitarism remains a significant long-term complication following Gamma Knife radiosurgery for pituitary adenomas, with reported rates ranging from 0% to 66% across studies, emphasizing the critical need for vigilant endocrine follow-up and individualized management strategies [15]. Our cohort of 137 patients demonstrated a female predominance [58.39%], a mean age of 50.7 years, and a median tumor volume of 3.51 cm³. NFPAs [60.58%] were the most prevalent, followed by prolactinomas [21.9%] and GH-secreting tumors [16.79%], with Cushing's disease being exceedingly rare [0.73%]. This distribution aligns with broader epidemiological trends, where NFPAs represent the majority of pituitary tumors [16, 17]. However, the near-absence of Cushing's disease contrasts sharply with **Cordeiro *et al.*** [10], who reported 25.6% of their cohort as Cushing's cases. This discrepancy may reflect regional differences in disease prevalence or selection bias, as our study excluded patients with prior radiotherapy, potentially omitting refractory Cushing's cases requiring multiple interventions. The median tumor volume [3.51 cm³] in our cohort is consistent with prior studies utilizing GKRS for residual or recurrent adenomas [17, 18].

Notably, **Gopalan *et al.*** [19] observed that tumors >5 cm³ were associated with higher progression rates, suggesting that our intermediate tumor volumes may represent a subset where GKRS balances efficacy and safety.

Pollock *et al.* [20] reported a higher median volume [4.0 cm³], potentially reflecting differences in surgical referral patterns or earlier GKRS adoption in our cohort. The predominance of NFPAs underscores their recalcitrance to medical therapy, necessitating adjuvant radiosurgery [21, 22].

In our study, 84.67% of patients required a single GKRS session, achieving tumor control in 91.97% of cases. The mean margin dose [15.8 Gy] and prescription isodose [40.7%] align with established protocols [23, 24].

The high tumor control rate mirrors **Gabri *et al.* [25],** who reported 86% 5-year progression-free survival [PFS], and **Sheehan *et al.* [16],** with 93.4% control. However, our margin dose was lower than Pollock et al. [20] [16 Gy] and higher than **Lee *et al.* [21]** [12 Gy], suggesting institutional variability in dosing strategies. Despite these differences, the consistency in tumor control across studies reinforces GKRS as a robust modality for residual or recurrent adenomas.

The 8.03% progression rate in our cohort is comparable to **Sun *et al.* [18]** [10%] and **Gabri *et al.* [25]** [14%]. Tumor progression was more frequent in larger tumors, a finding corroborated by **Gopalan *et al.* [19]** and **Pollock *et al.* [20].**

Notably, **Lindberg *et al.* [26]** reported a 57% 5-year PFS after repeat GKRS, highlighting the challenges of managing recurrent tumors. Our low retreatment rate [13.87% second procedures] suggests that initial GKRS effectively delays progression in most cases, though long-term vigilance remains critical.

A significant reduction in hypothyroidism prevalence [73.72% to 58.39%, p=0.007] and improvements in FT3, FT4, TSH, cortisol, PRL, GH, and IGF-1 levels [p<0.001] were observed.

Gonadal hormones [FSH, LH, testosterone, estradiol] remained stable, contrasting with **Cordeiro *et al.* [10],** who reported new gonadotropin deficiencies in 24.3% of patients. This discrepancy may stem from differences in baseline pituitary function or radiation dosing to the hypothalamic-pituitary axis. The decline in hypothyroidism post-GKRS is paradoxical, as radiation typically exacerbates pituitary dysfunction. However, tumor shrinkage may relieve mass effects on the pituitary, restoring thyrotroph function—a hypothesis supported by improvements in TSH and thyroid hormone levels.

Similar trends were noted by **Yu *et al.* [1],** though their hypothyroidism incidence [12%] was lower, possibly due to stricter dose constraints. The stability of gonadal hormones aligns with **Regal *et al.*[27],** who found preexisting deficiencies more predictive than GKRS effects. However, **Webb *et al.* [28]** emphasized that hormonal normalization does not always translate to quality-of-life improvements, a dimension absent in our study but critical for complete patient care.

Our findings demonstrate a significant reduction in new-onset hypopituitarism from 36.5% pre-treatment to 13.14% post-treatment, which aligns with and extends the insights from contemporary literature on radiation-induced pituitary complications. Comparative studies consistently highlight hypopituitarism as the most frequent adverse radiation event in pituitary adenoma treatments, with incidence rates ranging from 16.9%[29], 20.7%[1], and 32%[25] across their investigations. Notably, studies by **Yu *et al* [1], Graffeo *et al.* [30],** and **Wei *et al.* [29]** identified critical predictors such as mean dose, biological effective dose, and tumor volume as significant determinants of endocrine dysfunction.

Patients with hypothyroidism had significantly larger tumors [4.2 vs. 2.5 cm^3, p<0.001], a finding consistent across multiple studies. Pollock et al. [20] identified a 4.5-fold increased risk of hypopituitarism in tumors >4 cm^3, while **Gopalan *et al.* [19]** linked larger volumes to progression. Scientifically, larger tumors may require higher radiation doses or broader fields, inadvertently damaging adjacent pituitary tissue. **Sicignano *et al.* [24]** further implicated dose-volume parameters, showing that mean pituitary gland doses >15.7 Gy increased dysfunction risk. Our data suggest tumor volume serves as a surrogate for radiation exposure to healthy glandular tissue, emphasizing the need for precise dosimetry in larger lesions.

Univariate analysis identified tumor progression as protective [OR: 0.210] and larger tumor volume as deleterious [OR: 1.42]. The inverse association with progression is counterintuitive but may reflect aggressive management of progressing tumors [e.g., repeat GKRS or surgery], which could mitigate hormonal sequelae. Conversely, **Yu *et al.*[1]** found tumor progression increased hypopituitarism risk [HR=3.594], highlighting the complexity of this relationship. Larger tumor volume as a risk factor aligns with **Pollock *et al.* [20] and Graffeo *et al.* [30],** though the latter emphasized mean gland dose over volume.

Notably, radiation dose parameters [margin/maximum dose] did not correlate with hypothyroidism in our cohort, conflicting with **Graffeo *et al.* [30],** who identified mean gland dose as critical. This divergence may arise from differences in targeting: our study focused on tumor margins, whereas **Graffeo *et al.*** assessed glandular exposure. These findings underscore the multifactorial nature of hypopituitarism, where anatomical, dosimetric, and tumor-related factors interact.

Conclusions:

Gamma Knife Radiosurgery is an effective treatment for pituitary adenomas, achieving a tumor control rate of 91.97% with a relatively low retreatment rate. In our study, new-onset hypopituitarism was observed in 13.14% of patients post-GKRS—a significant reduction compared to the pretreatment rate of 36.5%. Endocrine evaluations revealed that thyroid and growth hormone axes showed significant improvement, while gonadal and adrenal axes remained largely stable. Larger tumor volume and tumor progression were identified as independent predictors of hypothyroidism. These findings underscore the importance of individualized dosimetry and long-term endocrine surveillance to balance tumor control with preservation of pituitary function.

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