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Hypopituitarism after Gamma Knife radiosurgery for pituitary adenomas: a multicenter, international study

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Abstract

OBJECTIVE—Recurrent or residual adenomas are frequently treated with Gamma Knife radiosurgery (GKRS). The most common complication after GKRS for pituitary adenomas is hypopituitarism. In the current study, the authors detail the timing and types of hypopituitarism in a multicenter, international cohort of pituitary adenoma patients treated with GKRS.

METHODS—Seventeen institutions pooled clinical data obtained from pituitary adenoma patients who were treated with GKRS from 1988 to 2016. Patients who had undergone prior radiotherapy were excluded. A total of 1023 patients met the study inclusion criteria. The treated lesions included 410 nonfunctioning pituitary adenomas (NFPAs), 262 cases of Cushing's disease (CD), and 251 cases of acromegaly. The median follow-up was 51 months (range 6–246 months). Statistical analysis was performed using a Cox proportional hazards model to evaluate factors associated with the development of new-onset hypopituitarism.

RESULTS—At last follow-up, 248 patients had developed new pituitary hormone deficiency (86 with NFPA, 66 with CD, and 96 with acromegaly). Among these patients, 150 (60.5%) had single and 98 (39.5%) had multiple hormone deficiencies. New hormonal changes included 82 cortisol (21.6%), 135 thyrotropin (35.6%), 92 gonadotropin (24.3%), 59 growth hormone (15.6%), and 11 vasopressin (2.9%) deficiencies. The actuarial 1-year, 3-year, 5-year, 7-year, and 10-year rates of hypopituitarism were 7.8%, 16.2%, 22.4%, 27.5%, and 31.3%, respectively. The median time to hypopituitarism onset was 39 months.

In univariate analyses, an increased rate of new-onset hypopituitarism was significantly associated with a lower isodose line ($p = 0.006$, HR = 8.695), whole sellar targeting ($p = 0.033$, HR = 1.452), and treatment of a functional pituitary adenoma as compared with an NFPA ($p = 0.008$, HR = 1.510). In multivariate analyses, only a lower isodose line was found to be an independent predictor of new-onset hypopituitarism ($p = 0.001$, HR = 1.38).

CONCLUSIONS—Hypopituitarism remains the most common unintended effect of GKRS for a pituitary adenoma. Treating the target volume at an isodose line of 50% or greater and avoiding whole-sellar radiosurgery, unless necessary, will likely mitigate the risk of post-GKRS hypopituitarism. Follow-up of these patients is required to detect and treat latent endocrinopathies.

Keywords

hypopituitarism; pituitary adenoma; Cushing's disease; acromegaly; stereotactic radiosurgery

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Pituitary adenomas are among the most common intracranial primary tumors, representing as much as 10%–20% of all of brain tumors.[3,7,8] These mostly benign lesions can be classified as either nonfunctioning pituitary adenomas (NFPAs) or functioning pituitary adenomas (FPAs)[22,23] based on clinically and biochemically evident endocrine secretory activity.

With the exception of prolactinomas, most patients with symptomatic NFPAs and FPAs initially undergo resection. After resection, recurrence or progression of a known residual lesion can occur in as many as 10%–50% of pituitary adenomas.[6] In FPA patients, such recurrence/progression can lead to a persistent hypersecretory state and related systemic morbidity. Historically, fractionated radiation therapy (RT) was used to treat patients with recurrent or progressive adenomas. However, over the past 2–3 decades, stereotactic radiosurgery (SRS), predominantly with the Gamma Knife, has been increasingly employed in the management of such patients.[2,14,19,28,39]

Following SRS, delayed onset of hypopituitarism (any axis) occurs in 20%–100% of patients.[5,21,37] Other SRS-related adverse effects, such as radiation-induced optic neuropathy and other cranial deficits, have been described. Radiological control of tumor growth has been reported to exceed 90% in most series of patients treated at high-volume centers, while the endocrine remission (a normal hormone level without medical management) is achieved in 50%–60% of patients with Cushing's disease (CD) and acromegaly.[12] To date, published studies of SRS-induced hypopituitarism have largely been single-center series with a relatively low statistical power and limited follow-up.[10,13,27,31,40] In the current study, we seek to better define the timing and nature of hypopituitarism after Gamma Knife radiosurgery (GKRS) and identify prognostic factors for its occurrence in a large multicenter cohort through the International Gamma Knife Research Foundation (IGKRF).

Methods

Study Coordination

As part of a multicenter international effort, 17 centers from the IGKRF identified pituitary adenoma patients treated with GKRS between 1988 and 2016. Inclusion criteria included a diagnosis of NFPA, FPA (CD or acromegaly), and at least one imaging study and a minimum 6-month clinical follow-up. Patients who had undergone previous RT were excluded. Data were pooled by the IGKRF study coordinator, checked for errors, and then sent to the study coordinating site principal investigator at the University of Virginia. The study was approved by institutional review boards at the individual participating centers.

Patients' Attributes

A total of 1023 patients constituted this multicenter retrospective cohort. Patients were from the 17 centers: University of California 47, Beaumont Health System 6, Ain Shams University and Gamma Knife Center Cairo 16, Benha University 4, Cleveland Clinic 28, Ruber International Hospital 44, NYU Langone Medical Center 14, University of Pennsylvania 16, Na Homolce Hospital 117, Charles University and General University

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Hospital 4, Université de Sherbrooke 13, Taipei Veterans General Hospital 98, University of Pittsburgh 183, University of Virginia 392, West Virginia University 3, and Yale University 38.

Table 1 details the patient demographics and characteristics. Overall 642 (62.8%) had one surgery (craniotomy and resection or transsphenoidal adenomectomy), 296 (28.9%) had multiple resections, 72 patients (7%) had upfront GKRS, and 13 patients (1.3%) had indeterminate treatment.

Endocrine Baseline Information

The diagnosis of pituitary adenoma was based on clinical, radiological, and endocrine findings. Patients who had undergone a previous surgery had their pathological diagnosis established at each center. Prior to GKRS, patients also underwent a comprehensive endocrine evaluation that included 24-hour urinary free cortisol, adrenocorticotropic hormone (ACTH), serum cortisol, follicle-stimulating hormone (FSH), insulin-like growth factor–1 (IGF-1), growth hormone (GH), testosterone, estradiol, prolactin, thyroid-stimulating hormone (TSH), free thyroxin (T4), and clinical evaluation for diabetes insipidus (DI).

Because the multicenter nature of this cohort mandated gathering patient information from different centers, we therefore relied on clinical evaluations and hormone assessments that were conducted at the individual institution and laboratories and/or provided by primary care physicians in different healthcare facilities.

GKRS Technique

The GKRS technique for the treatment of patients with pituitary adenomas has been described in detail.[33] In brief, a stereotactic Leksell stereotactic Gamma Knife frame was placed after the patient had received local anesthesia coupled with monitored sedation as needed. To better elucidate the pituitary adenoma, we used an MRI protocol of thin slices (1 mm) before and after contrast administration, often combined with fat suppression. This multicenter, international study involved different institutions with clinical data spanning a few decades. As such, a variety of Gamma Knife models were used, including model U, model C, Perfexion, and Icon, depending on the time of treatment and the treatment site. The recurrence or progression of a pituitary adenoma, postoperative residual (more frequent with cavernous sinus invasion), and hypersecretory state (FPA) were common indications for GKRS.

The GKRS dose plan was determined by a team made up of a neurosurgeon, radiation oncologist, and medical physicist, and depended on tumor type, tumor volume, prior cranial nerve deficits, and proximity of the lesion to the brainstem and optic apparatus. At many centers, patients with FPAs were encouraged to discontinue any antisecretory medication prior to GKRS, a clinical protocol that started around year 2001. Dopamine agonists were discontinued 4 weeks before GKRS and cortisol-lowering drugs and somatostatin analogs were discontinued 6–8 weeks before GKRS.[28,29,33] The median margin dose to FPAs was 25 ± 6.5 Gy (range 3.0–40.0 Gy), and the median margin dose to NFPAs was 16.0 ± 4.23

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Gy (range 5–35 Gy). The median follow-up duration was 51 months (range 6–246 months). Table 2 summarizes the patient characteristics and GKRS parameters.

Follow-Up Protocol

Follow-up schedules differed to some extent among the different centers. A general scheme involved a scheduled follow-up visit every 6 months after GKRS during the 1st year or two and then annually thereafter. Neurosurgical, endocrine, and radiological encounters were generally scheduled at the same time. Patients had clinical evaluation performed by both neurosurgeons and endocrinologists, underwent dedicated MRI brain scanning, and had hormone studies performed as routine at regular visits.

Endocrine follow-up visits included periodic laboratory tests for serum cortisol, ACTH, FSH, IGF-1, GH, testosterone, estradiol, prolactin, TSH, T4, and clinical assessment for DI. New-onset post-GKRS hypopituitarism was defined as a pituitary hormone deficiency (of those listed above) that required hormone replacement at any time after GKRS. Hypopituitarism that developed prior to the time of GKRS was found in 383 patients (37.4%). In detail, a corticotroph deficiency was defined as any value below the normal range in the investigations of serum cortisol. A thyrotroph deficiency was diagnosed based on a low T4 with a normal or decreased TSH hormone level; a gonadotroph deficiency was defined as low or normal gonadotropin levels and low plasma testosterone in men and amenorrhea with low plasma estradiol in premenopausal women; and a GH deficiency was defined as a low IGF1 or a subnormal GH response during a stimulation test adjusted by the patient age and sex.

Tumor control was defined as no growth (tumor volume with a change within ± 10% of the pretreatment volume) or shrinkage (> 10%) of pituitary adenomas, and radiological failure was considered tumor growth of > 10% of the pretreatment volume demonstrated on MRI brain scans at routine follow-up visits.[35]

Statistical Analysis

Statistical analysis was performed using a Cox proportional hazards regression model to evaluate prognostic factors associated with the time to new-onset hypopituitarism following GKRS. The assumption of proportional hazard was confirmed using a log-minus-log method prior to the analysis. Variables with a p value ≤ 0.1 in all univariate analyses were subsequently enrolled in a multivariate analysis. The one-way ANOVA was used to determine whether there were any statistically significant differences between the means of more than two unrelated groups in relation to tumor type, isodose line, and status of whole-sellar treatment. Kaplan-Meier plots were employed to assess the new onset of hypopituitarism. Logistic regression was used to evaluate radiological tumor control. All statistical analyses were conducted using a commercially available statistical package (IBM SPSS version 24.0). All the statistical studies were two-sided and a p value < 0.05 was deemed statistically significant.

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Results

Time of New-Onset Hypopituitarism Following SRS

At last follow-up, 248 patients (24.2%) had developed new hypopituitarism. Among them, 150 patients had a single hormonal deficiency and 98 had multiple hormone deficiencies; only 7 patients developed panhypopituitarism. Hypopituitarism occurred in 86 NFPA (34.68%), 66 CD (26.61%), and 96 acromegalic (38.71%) patients. The actuarial hypopituitarism rates at 1, 3, 5, 7, and 10 years were 7.8%, 16.2%, 22.4%, 27.5%, and 31.3%, respectively. The median time to onset of new hypopituitarism was 39 months (range 3–171.60 months). New hormonal changes included 82 cortisol (21.6%), 135 thyrotropin (35.6%), 92 gonadotropin (24.3%), 59 growth hormone (15.6%), and 11 vasopressin (2.9%) deficiencies. Figure 1 indicates new endocrine deficiencies by adenoma type.

In the univariate analysis, an increased rate of new-onset hypopituitarism was significantly associated with the following factors: lower isodose line prescribed ($p = 0.006$, HR = 8.695), whole-sellar targeting ($p = 0.033$, HR = 1.452), and an FPA as opposed to an NFPA ($p = 0.008$, HR = 1.510). In multivariate analyses, treatment with a lower isodose line was associated with an increased rate of new-onset hypopituitarism ($p = 0.001$, HR = 1.38). For every 10% reduction of the isodose line treatment, there was an accompanying increased risk rate of 27% of new hypopituitarism after GKRS. Previous surgery, hypopituitarism before GKRS, margin and maximum dose, cavernous sinus invasion, suprasellar extension, and treated volume were factors not associated with post-GKRS hypopituitarism. Extended follow-up did not show any appreciably increased risk. Table 3 summarizes the statistical analyses.

Patient demographics, tumor characteristics, planning treatment, time to new-onset hypopituitarism, and radiological control stratified by isodose line are displayed in Table 4. The most statistically significant variable was the decreasing treatment isodose line, which was associated with an increasing rate of risk of new-onset endocrine deficiencies.

The majority of the patients (n = 771) were treated with a 50% isodose line; of these, 342 (44.4%) had NFPAs, 186 (24.1%) had CD, and 243 (31.5%) had acromegaly. One hundred forty-eight patients were treated with an isodose line greater than 50%; of these, 6 patients (4.1%) had NFPAs, 54 (36.5%) had CD, and 88 (59.5%) had acromegaly. One hundred three patients were treated with an isodose line less than 50%; of these, 62 (60.1%) had NFPAs, 22 (21.4%) had CD, and 20 (19.4%) had acromegaly. The Kaplan-Meier plot (Fig. 2) shows how patients with FPAs in relation to NFPAs are more prone to developing new-onset hypopituitarism after GKRS, and the other Kaplan-Meier plot (Fig. 3) illustrates the increased risk of lower isodose line treatments on the onset of new hypopituitarism.

Radiological Response

The median imaging follow-up period was 51 months (range 6–246 months). At last follow-up, tumor control was achieved in 985 patients (96.3%), and 38 patients (3.7%) had adenoma progression after GKRS. Of those with adenoma progression, 23 had NFPAs, 11 had CD, and 4 had acromegaly. In the logistic regression analysis, improved tumor control rates were related to an increasing margin dose and maximum dose, FPA versus

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NFPA, no suprasellar extension, and reduced treatment volume (Table 5). We did not find any statistical correlation between tumor control and hypopituitarism after GKRS in logistic regression analysis (p = 0.636; OR = 1.004, 95% CI 0.986–1.023).

Discussion

The first scientific study to investigate the overall prevalence and incidence of hypopituitarism in a population was done in Spain with a sample size of 146,000 people. The first survey found the overall prevalence of hypopituitarism to be 29 per 100,000, and the second survey found it to be closer to 45.5 per 100,000.[30] Hypopituitarism is defined as a biochemical deficiency associated with one or more hormonal axes of the anterior and/or posterior pituitary gland. It can occur as a result of dysfunction of the pituitary gland or as a result of hypothalamic damage. Hypopituitarism can be primary due to pituitary dysfunction or secondary to other disease such as pituitary adenomas. These tumors can cause hypopituitarism because of adenoma growth and resulting compression on the normal pituitary gland and stalk. It can also arise as a result of iatrogenic injury to the normal neuroendocrine structures during treatments such as surgery, radiosurgery, and RT.[5,18]

If undetected and uncorrected, hypopituitarism can have appreciable morbidity and even mortality. A recent meta-analysis demonstrated that hypopituitarism is associated with an overall excess mortality. This could be explained by metabolic changes associated with hormonal imbalance, radiation-induced vasculopathy or atherosclerosis related to pituitary insufficiency, and prothrombotic states. Some studies of hypopituitary patients have shown that younger age and female sex are risk factors for a high mortality rate.[15,20]

Patients who develop hypopituitarism also have a poor quality of life (QOL). This impact on QOL tends to be more severe in patients with CD and acromegaly than in those with NFPA and prolactinomas. The presence of multiple pituitary deficiencies further worsens QOL. Despite optimal endocrine replacement, QOL often remains below reference values. These QOL studies on hypopituitarism reveal the importance of long-term follow-up of these patients, proper diagnosis, and adequate hormonal replacement when necessary.[16,38]

In the current study, we found that 24.2% of patients developed new-onset hypopituitarism following GKRS, and this is comparable to rates published in several prior SRS reports.[32,33] This incidence is also lower than the historic risk of hypopituitarism following RT, which is believed to be as high as 50%.[36] The timing for new-onset hypopituitarism is typically within 5 years after SRS, whereas post-RT hypopituitarism typically occurs even before 1–10 years after treatment.[21]

The prescription of an increasing isodose line portended a lower risk of new-onset hypopituitarism after adjusting for other parameters, including age at GKRS, margin dose, and adenoma type. The use of a much lower isodose line at the margin can lead to a dramatic increase in the maximum dose delivered to the target, although this would also increase the total energy delivered to normal surrounding structures[34] such as the normal pituitary gland, pituitary stalk, and hypothalamus.

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Lower isodose plans likely conveyed a poor gradient index, and they are a surrogate for an increased radiosurgical dose delivered to critical structures, as can be seen in Table 4; despite a lower median margin dose (15 Gy), isodose lines less than 50% had a maximum dose of 50 Gy, compared with a prescribed isodose line of 50% or more than 50% that had median maximum doses of 40.1 Gy and 30.84 Gy, respectively. The established rationale for prescribing a 50% or higher isodose line in GKRS is that the dose distribution maximizes the gradient just beyond the tumor edge and thus minimizes the dose to adjacent organs at risk. Achieving conformal coverage of the target with a higher isodose line would enable the tumor to receive more homogeneous high-dose radiation with an increased mean dose. Since the adenoma is receiving an increased mean dose, the treatment dose can be optimized by reducing the maximum dose delivered to the center of the target while maintaining the same dose in the margin, and the surrounding normal tissues can receive less radiation, thereby possibly reducing the risk of hypopituitarism.

Comparing Hypopituitarism From Resection, RT, and SRS

The incidence of hypopituitarism following surgery varies from 10% to 25%.[9,26] Post-resection hypopituitarism has been reported to be associated with larger adenoma size, the degree to which the adenoma invades the cavernous sinus, the quantity of normal gland remaining after resection, and the experience of the treating neurosurgeon.[1,25] Endocrinopathies of the anterior pituitary gland are the most common complication after resection and have an incidence of 2%–22%. DI following resection occurs in 0.4%–15% of cases but is typically transient (3%) or less permanent.[9,25,26]

RT has also been associated with hypopituitarism in 50%–100% of cases. The typical timing of hypopituitarism onset after RT is as soon as 6–12 months, with a range of 1–10 years.[4,36] Endocrine axes affected after RT are most common, in a decreasing order of frequency: GH, gonadotropins, ACTH, and TSH. Hyperprolactinemia can also occur due to hypothalamic damage leading to reduced dopamine release. Hyperprolactinemia has been described in both sexes and in individuals of all ages but is mostly seen in young women after intensive irradiation and is usually subclinical. Factors that portend a greater risk of post-RT hypopituitarism are higher-dose treatments and the time elapsed since irradiation.[4,36]

In a study by Feigl et al.,[11] GKRS seemed a safe and effective treatment for patients with residual and recurrent pituitary adenomas. The rate of pituitary insufficiency after GKRS is lower than that after conventional RT. The results of the present study show that patients in whom the pituitary stalk and pituitary gland receive a higher mean point dose are more likely to develop pituitary insufficiencies after GKRS than those who receive a lower dose and, furthermore, that the dose delivered to the hypothalamus is usually very low. However, long-term follow-up studies of GKRS-treated pituitary tumors are scarce. Previous studies have reported rates of new hormone deficiency ranging between 0% and 40%.[24] Gopalan et al.[12] found a 39% rate of new hormone deficiency, with the most common new hormone deficits being thyroid hormone and GH; the actuarial rate of endocrinopathy in their study increased from 12.5% at 24 months to 50.7% at 120 months, with an estimated mean time to loss of pituitary function of 112 months. In a recent study, Xu et al.[41] reported

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hypopituitarism in 30% of patients following GKRS; they found that a higher margin dose and suprasellar extension of a pituitary adenoma were risk factors associated with new onset of endocrine deficiencies.

An increased risk of hypopituitarism has been shown to be associated with the radiosurgical targeting of the whole sella in selected patients with CD in whom no discrete adenoma was identified on MRI.[17] The current study validates prior findings. Intuitively, patients in whom the remaining normal gland received the prescription dose should be carefully followed for post-SRS hypopituitarism. Unlike following resection, post-SRS posterior pituitary insufficiency occurred in only 4.6% of patients. Anterior pituitary deficiency in our study occurred more commonly than posterior pituitary deficiency, and the ratio of anterior pituitary deficits to posterior pituitary deficits was 20 to 1.

We found that only 15.3% of all the patients with new-onset hypopituitarism developed new endocrine deficits in a time frame of more than 5 years after SRS. While infrequent, very delayed–onset hypopituitarism after GKRS can occur, and this does underscore the importance of longitudinal endocrine follow-up of these patients to detect deficiencies and treat them with appropriate replacement therapy to minimize the impact in the QOL and reduce the risk of mortality.

Study Limitations

While this study is composed of multicenter data and represents the largest such study to date, it does have limitations. The study has the limitations inherent in a retrospective design, including selection bias and treatment, as well as follow-up variations. Participating centers represent tertiary referral centers that draw patients from afar. While every attempt was made to have the patients undergo follow-up with their treating physicians, some patients chose to have follow-up with their local physicians, and the information gathered in such cases was therefore based on endocrine testing by local clinicians. While all patients were treated with a common radiosurgical platform, the treatments spanned several decades, during which the Gamma Knife technology, neuroimaging protocols, and radiosurgical techniques evolved. Also, post-GKRS endocrine testing was performed at the discretion of the treating team, and the timing of the testing was not always uniform; irregularities in endocrine testing time could have impacted the time to new-onset hypopituitarism. Moreover, endocrine testing assays and normal ranges have changed over the study period. Thus, the current study may underestimate the degree of hypopituitarism. While there are limitations to the current study, the delayed effect of hypopituitarism after GKRS makes a prospective study of this topic logistically challenging.

Conclusions

Hypopituitarism remains the most common adverse effect of GKRS for pituitary adenoma patients. Treating the target volume at an isodose line of 50% or greater and avoiding whole-sellar radiosurgery unless necessary will likely mitigate the risk of post-GKRS hypopituitarism. While the majority of hypopituitarism occurs within the first 1–5 years after GKRS, delayed hypopituitarism, even beyond 10 years, can occur, and therefore,

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longitudinal follow-up of these patients is required to detect and replace any endocrine deficiencies when appropriate.

Disclosures

Dr. Lunsford reports being a consultant for Insightec DSMB and having direct stock ownership in Elekta. Dr. Grills reports having direct stock ownership in Greater Michigan Gamma Knife, where she is on the executive board of directors, and she reports receiving, through her institution, research funding from Elekta that is unrelated to the present study.

ABBREVIATIONS

ACTH	adrenocorticotropic hormone
CD	Cushing's disease
DI	diabetes insipidus
FPA	functioning pituitary adenoma
FSH	follicle-stimulating hormone
GH	growth hormone
GKRS	Gamma Knife radiosurgery
IGF-1	insulin-like growth factor–1
IGKRF	International Gamma Knife Research Foundation
NFPA	nonfunctioning pituitary adenoma
QOL	quality of life
RT	radiation therapy
SRS	stereotactic radiosurgery
TSH	thyroid-stimulating hormone
T4	free thyroxin

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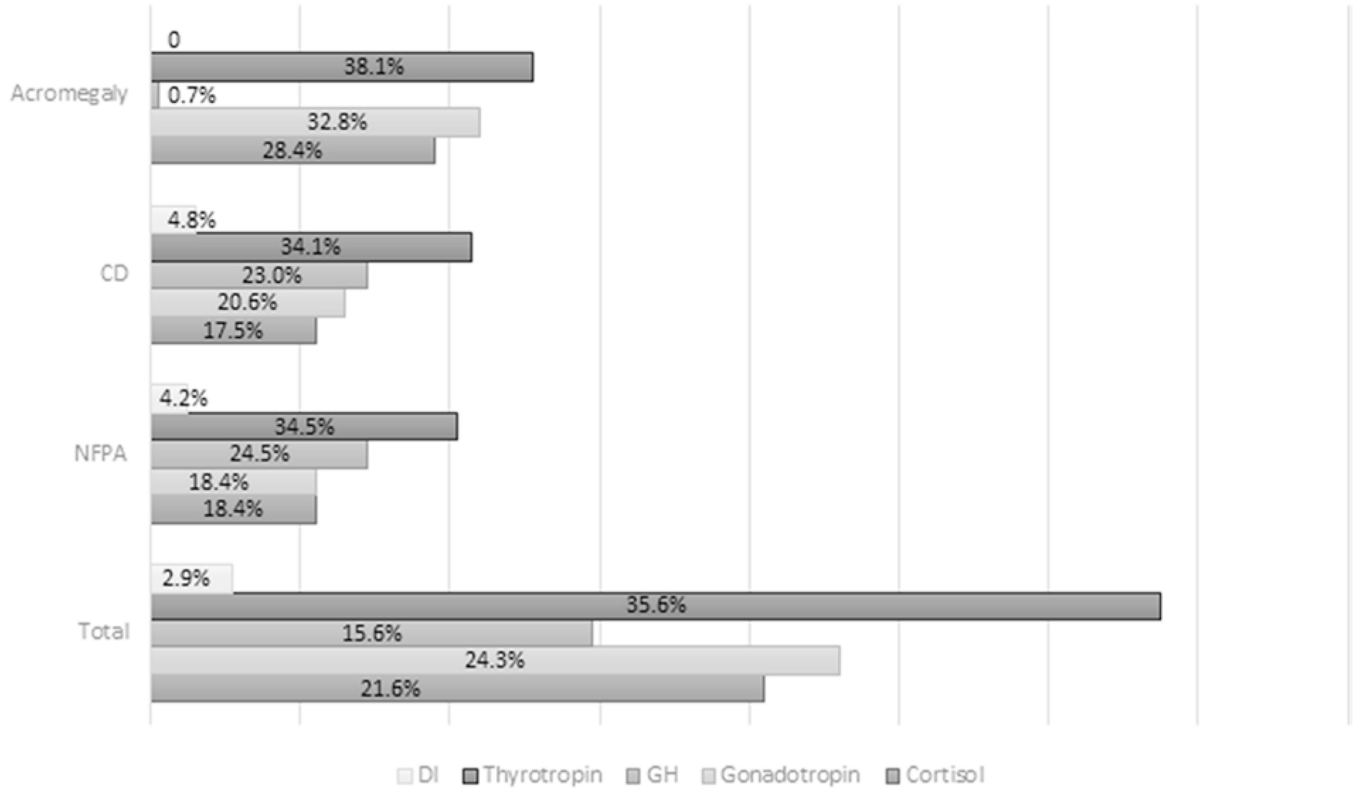

FIG. 1.
New hormone deficiencies in patients with different types of adenoma.

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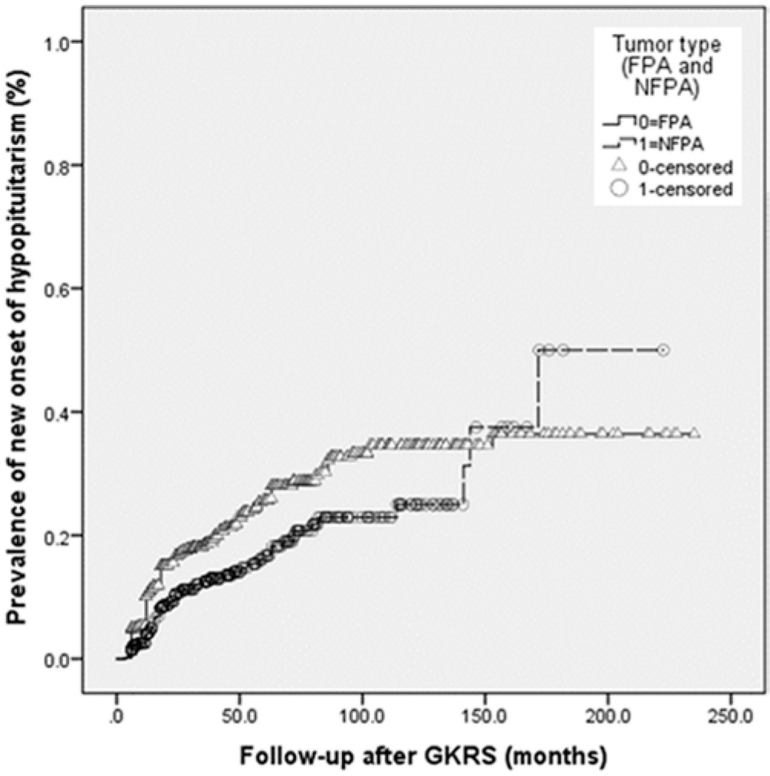

FIG. 2.
Kaplan-Meier plot of time to new-onset hypopituitarism related to NFPA and FPA.

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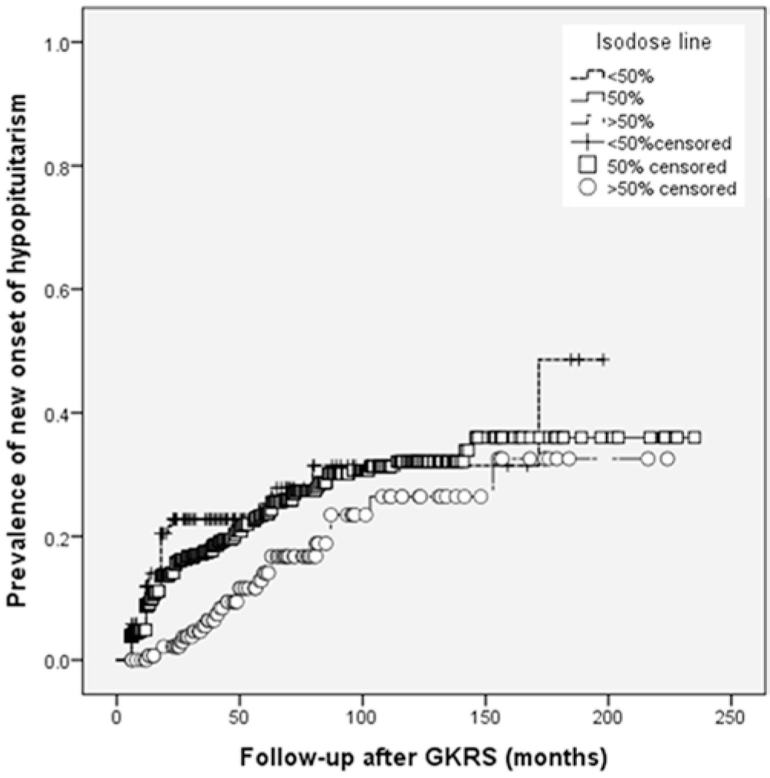

FIG. 3.

Kaplan-Meier plot of time to new-onset hypopituitarism in relation to the isodose line prescription.

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TABLE 1.

Patient demographics and characteristics

Variable	Patients		Patients w/New Hypopituitarism		Patients w/o New Hypopituitarism	
	No.	%	No.	%	No.	%
Total	1023	100	248	24.2	775	75.8
Male	437	42.7	116	26.5	454	73.5
Female	586	57.3	132	22.5	454	77.5
NFPA	410	40.1	86	21.0	324	79.0
CD	262	25.6	66	25.2	196	74.8
Acromegaly	351	34.3	96	27.4	255	72.6
Prior ops	938	91.7	233	24.8	705	75.2
Suprasellar extension	200	19.6	49	24.5	151	75.5
CS invasion	584	57.1	142	24.3	442	75.7
Whole-sellar Tx	153	15.0	49	32.0	104	68.0

CS = cavernous sinus; Tx = treatment.

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TABLE 2.

Summary of patients and GKRS characteristics

Variable	Entire Study		Patients w/ New Hypopituitarism		Patients w/o New Hypopituitarism	
	Median	Range	Median	Range	Median	Range
Age at SRS, yrs	47	12–92	44.51	14–88	48	12–92
Prior op, no.	1	0–7	1	0–3	1	0–7
Treated vol, cm^3	2.47	0.1–58.1	2.8	0.1–37.3	2.3	0.1–58.1
Margin dose, Gy	20	3–40	20	3–40	20	5–40
Max dose, Gy	40	10–83.30	41.29	10–80	40	10–83.3
Isocenters	7	1–40	8.54	1–23	7	1–40
IDL, %	50	20–90	50	20–90	50	20–90

IDL = isodose line.

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TABLE 3.

Univariate and multivariate analyses of potential prognostic factors contributing to the time of new-onset hypopituitarism after SRS

	Univariate Analysis				Multivariate Analysis			
			95% CI				95% CI	
Variable	p Value	HR	Lower	Upper	p Value	HR	Lower	Upper
Age at SRS	0.053	0.991	0.982	1.00	0.082	0.99	0.979	1.001
CS invasion	0.983	0.997	0.759	1.309				
Suprasellar extension	0.879	1.028	0.722	1.462				
Whole-sellar Tx	0.033	1.452	1.031	2.047	0.117	1.321	0.933	1.87
Margin dose	0.816	0.998	0.979	1.017				
Max dose	0.331	1.005	0.995	1.014				
Hypopituitarism at time of GKRS	0.189	0.822	0.614	1.101				
Tx vol	0.829	1.003	0.973	1.035				
IDL	0.006	8.695	1.872	40.00	0.001	1.38	1.14	1.67
FPA vs NFPA	0.008	1.51	1.113	2.048	0.871	1.07	0.471	2.434
Previous op	0.085	1.669	0.932	2.99				
No. of previous ops	0.736	1.035	0.848	1.263				

Analyses performed using Cox regression models.

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TABLE 4.

Patient demographics, tumor characteristics, planning treatment, time to new-onset hypopituitarism, and tumor control by isodose line

Frequencies by IDL	**IDL <50 Gy**	**IDL 50 Gy**	**IDL >50 Gy**
No. of patients	103	771	148
Median age, yrs	49	47	45.31
Prior op, no.	97 (94.2%)	712 (92.3%)	128 (86.5%)
Median treated vol, cm^3	3.564	3.597	3.602
CS invasion, no.	60 (58.3%)	469 (60.8%)	54 (36.5%)
Suprasellar extension, no.	22 (21.4%)	166 (21.5%)	11 (7.4%)
Whole-sellar Tx, no.	8 (7.8%)	135 (17.5%)	10 (7.0%)
Median margin dose, Gy	15.00	20.00	20.00
Median max dose, Gy	50.00	40.10	30.84
Median no. of isocenters	5.00	8.00	8.00
New-onset hypopituitarism, no.	30 (29.1%)	190 (24.6%)	28 (18.9%)
Median time to new hypopituitarism (range), mos	13 (4.70–171.60)	18 (3–143.9)	46.50 (13–153)
Mean time to new hypopituitarism, mos	25.2285	50.68	53.73
Radiological control, no.	94 (91.3%)	747 (96.9%)	143 (96.6%)

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TABLE 5.

Factors related to tumor control

	Logistic Regression			
			95% CI	
Factor	**p Value**	**OR**	**Lower**	**Upper**
Age at GKRS	0.766	0.997	0.975	1.019
CS invasion	0.806	0.922	0.48	1.768
Suprasellar extension	0.002	2.912	1.482	5.721
Whole-sellar Tx	0.401	1.595	0.537	4.739
Margin dose	<0.001	0.877	0.821	0.936
Max dose	<0.001	0.946	0.917	0.976
New hypopituitarism	0.636	1.004	0.986	1.023
Treated vol	0.011	1.062	1.014	1.112
IDL	0.095	0.043	0.001	1.727
FPA vs NFPA	0.011	2.369	1.221	4.598
Isocenters	0.716	1.011	0.953	1.073
Previous op	0.493	1.656	0.392	7.001