RESEARCH

Long-term hormonal and imaging outcomes of adjunctive gamma knife radiosurgery in non-functioning pituitary adenomas: a single center experience

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Abstract

Purpose Gamma Knife Radiosurgery(GKRS) is an established modality for treatment of non-functioning pituitary adenomas(NFPA). The objective of the study was to assess long-term hormonal and imaging outcomes after adjunctive GKRS in patients with NFPA.

Methods A retrospective review of records of 109 patients with NFPA, from 1996 to 2020, who received adjunctive GKRS, was performed. Patients who had received GKRS as the primary modality of treatment for NFPA were not included.

Results Sixty-three (57.8%) patients were available for follow up at our institute. The median follow-up period was 47 months (range, 6–260). At a median time of 38 months (range, 8–97), 25 (39.7%) patients developed ≥ 1 new pituitary hormone deficiency. Median time to cortisol deficiency was 38 months (range, 8–55), thyroid hormone deficiency was 45.5 months (range, 12–97) and gonadotropin deficiency was 45 months (range, 21–75). The actuarial risk of developing a new pituitary hormone deficit at 1, 3, 5, 7, and 10 years was 2.5%, 11%, 26.3%, 28% and 29.7%, respectively. Adenoma size decreased in 36 (57.1%) patients, remained unchanged in 19 (30.2%) patients, and increased in 8 (12.7%) patients. Overall tumor control rate was 87.3%. Endocrinopathy-Free Survival was 47.1%, and tumor Progression-Free Survival was 93.3%, at 5 years. Five (4.6%) patients required additional treatment after GKRS. One (1.6%) patient each had worsening of headache, optic atrophy and cerebellar infarct after GKRS therapy.

Conclusion GKRS offers a safe adjunctive treatment modality, with satisfactory long-term preservation of hormone functions and a high rate of tumor control, in patients with NFPA.

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Introduction

Adenomas of the pituitary gland comprise 10–20% of all intracranial tumors, 30% of which are non-functioning pituitary adenomas (NFPA) [1]. Trans-sphenoidal surgery remains the first line of treatment in NFPA, as it provides rapid resolution of tumor mass-effect, and a likelihood of complete tumor excision [2, 3]. However, various studies have reported that 33–85% of patients with NFPA have residual tumors after surgical resection due to various tumor, technique and/or surgeon-related factors [1–6]. The recurrence rates in surgically treated NFPA vary from 10 to 20% in gross total resections, and 50 to 60% in subtotal resections [1, 4, 7, 8]. Thus, patients with NFPA may require additional surgery and/or adjuvant radiotherapy for the treatment of residual or recurrent disease.

Repeat surgery on the pituitary fossa is associated with higher perioperative and postoperative complications than those encountered during initial resection [9, 10]. Gamma Knife Radiosurgery (GKRS) is a safe and effective treatment modality that can be used as an adjunct for patients who undergo subtotal resection of NFPA, and for those with recurrent NFPA [5, 11, 12]. Less commonly, GKRS can also be used as a primary treatment modality in NFPA for patients with surgical comorbidities, advanced age, or for those with a personal preference [13, 14]. GKRS is associated with a lesser risk of hypopituitarism, radiation-induced secondary tumors, carotid stenosis, stroke, as well as neurocognitive side effects as compared to conventional radiotherapy [13].

There is relatively modest data on the long-term outcomes of GKRS on NFPA. In the present study, we retrospectively evaluated our experience with adjunctive GKRS in the management of patients with NFPA, with emphasis on hormonal and radiologic outcome. To the best of our knowledge, the present publication is the first of its kind from South Asia. We believe this evaluation of post-operative adjunctive GKRS in a sizable cohort of patients with NFPA will be a valuable addition to the literature.

Methods and materials

Study design

This retrospective study was conducted using a database of 109 patients with NFPA, who underwent adjunctive GKRS between 1996 and 2020, at the P. D. Hinduja Hospital and Medical Research Centre, Mumbai, India. Information related to the clinico-imaging characteristics, surgical data, laboratory parameters, follow-up, and outcomes of all the patients was collected by reviewing the individual case files in the medical record section. Patients with a post-GKRS follow-up of at least 6 months at our institute, and having had at least one neuroimaging in the 'follow-up cohort' were included in the study. Inclusion criteria were satisfied by 63 patients. Data was collated, tabulated, and analyzed statistically.

Patient characteristics

The follow-up cohort consisted of 39 male and 24 female patients, with a mean age of 47.3 ± 11.3 years at the time of GKRS, and a median follow-up period of 47 months (range, 6–260 months). All 63 patients received GKRS as an adjunctive therapy for residual or recurrent tumors. Forty (63.5%) patients had undergone adenoma resection surgery once and 23 (36.5%) patients had two surgeries prior to being subjected to GKRS. Median time to GKRS was 293 days (range, 69–1659 days) after the last surgery. Headache (25.4%), vision loss (23.8%) and double vision (6.3%) were the common symptoms prior to GKRS in the study group. Of the 15 patients with complaint of vision loss, 7 had bilateral partial loss of vision, 3 had partial loss of vision in the right eye, 4 had partial loss of vision in the left eye, and 1 patient had complete vision loss in the left eye. Thirty seven of the 63 patients (58.7%) had visual field defects prior to undergoing GKRS. 26 (70.3%) had bi-temporal hemianopia, 8 (21.6%) had unilateral temporal defects and 1 (1.6%) patient each had left homonymous hemianopia, bilateral severely constricted visual fields and bilateral few scattered defects. Two (3.2%) patients had third cranial nerve palsy, while 1 (1.6%) patient had optic nerve involvement (Table 1).

Endocrine evaluation & characteristics

All the patients had a periodic evaluation of adrenal (baseline serum cortisol with/without serum adrenocorticotropic hormone), thyroid (serum total or free T4, and serum thyroid stimulating hormone), and gonadal (serum follicle-stimulating hormone and serum luteinizing hormone, and serum testosterone in men) axes. Diagnosis of secondary hypocortisolism was established if 8 a.m. serum cortisol < 5 mcg/dL (137.9 nmol/L), or an inappropriately low/normal serum adrenocorticotropic hormone (ACTH) value (< 20 pg/ml, < 4.4 pmol/L) accompanying a decreased serum cortisol level, or a 1 h post-standard ACTH (using intravenous tetracosactide acetate 250 μg) serum cortisol of < 18 mcg/dL (496.5 nmol/L), or patient already receiving glucocorticoid replacement therapy. Patients with serum total T4 < 4.5 mcg/dL (57.9 nmol/L) or serum free T4 < 0.8 ng/dL (10.3 pmol/L), with serum thyroid stimulating hormone (TSH) < 4.5 mIU/L, or those on levothyroxine replacement therapy were diagnosed to have hypothyroidism.

Table 1 Pre-GKRS characteristics in the follow-up cohort

Characteristic	Value
Total patients, N	63
Age at GKRS in years, mean ± SD	47.3 ± 11.8
Gender, N(%)	
Male	39 (61.9)
Female	24 (38.1)
Indication for GKRS, N(%)	
Residual NFPA	60 (95.2)
Recurrent NFPA	3 (4.8)
Single surgery pre-GKRS, N(%)	
TSS	39 (61.9)
TCS	1 (1.6)
Two surgeries pre-GKRS, N(%)	
TSS + TSS	15 (23.8)
TSS + TCS	4 (6.3)
TCS + TSS	4 (6.3)
Time to GKRS after last pituitary surgery in days, median(range)	293 (69–1659)
Symptoms, N(%)	
Headache	16 (25.4)
Vision loss	15 (23.8)
Diplopia	4 (6.3)
Clinical signs, N(%)	
Visual field defects	37 (58.7)
CN III	2 (3.2)
CN II	1 (1.6)

CN cranial nerve, *GKRS* gamma knife radiosurgery, *NFPA* non-functioning pituitary adenomas, *SD* standard deviation, *TCS* trans-cranial surgery, *TSS* trans-sphenoidal surgery

Premenopausal women were diagnosed with hypogonadism if they had amenorrhea and both serum follicle-stimulating hormone (FSH) and serum luteinizing hormone levels (LH) were < 10 mIU/mL; while post-menopausal women were defined as gonadotropin deficient when serum LH was < 10 mU/L and serum FSH was < 30 mU/L. In men, gonadotropin deficiency was diagnosed if serum total testosterone level was < 3 ng/ml (10.4 nmol/L). Diagnosis of diabetes insipidus was made if the patient was receiving desmopressin. Sufficient data was not available regarding prolactin and growth hormone axes. Hypopituitarism was defined if the patient had any one of hypocortisolism, hypothyroidism, or hypogonadism. Panhypopituitarism was diagnosed if the patient had hypocortisolism, hypothyroidism, and hypogonadism.

Pre-GKRS, 25 (39.7%) patients did not have any hormonal deficiency. Among the remaining 38 (60.3%) patients, single endocrine axis was involved in 16 (25.4%) patients and various combinations of multiple axes involvement were seen in 22 (34.9%) patients. Panhypopituitarism was present in 11 (17.5%) patients (Table 2).

Table 2 Pre-GKRS endocrinopathy and radiological adenoma extensions in the follow-up cohort

Characteristic	Value
Endocrinopathy, N(%)	
No endocrinopathy	25 (39.7)
Only hypocortisolism	6 (9.5)
Only hypothyroidism	7 (11.1)
Only hypogonadism	3 (4.8)
Hypocortisolism+hypothyroidism	8 (12.7)
Hypocortisolism+hypogonadism	1 (1.6)
Hypothyroidism+hypogonadism	1 (1.6)
Hypocortisolism+hypothyroidism+hypogonadism	7 (11.1)
Hypocortisolism+hypogonadism+DI	1 (1.6)
Hypocortisolism+hypothyroidism+hypogonadism+DI	4 (6.4)
Tumour extension, N(%)	
Intra-sellar	7 (11.1)
Cavernous sinus only	32 (50.8)
Suprasellar only	11 (17.5)
Posterior only	2 (3.2)
Anterior only	1 (1.6)
Cavernous+Suprasellar	9 (14.3)
Cavernous+Suprasellar+Anterior+Infrasphenoid	1 (1.6)
Volume of NFPA pre-GKRS in cm³, mean ± SD	3.1 ± 2.5

DI diabetes insipidus, *GKRS* gamma knife radiosurgery, *NFPA* non-functioning pituitary adenomas, SD-Standard Deviation

Imaging characteristics

The NFPA imaging patterns were assessed by Magnetic Resonance Imaging (MRI, all available T1-weighted sequences), in axial, coronal, and sagittal planes. Tumor volumes were calculated from the volume of an oblate spheroid, using the Di Chiro and Nelson formula: (anteroposterior dimension × vertical dimension × horizontal dimension in cm) × (π/6). Given the irregular shape of some tumors, volume measurement should be considered only a rough estimate of the actual tumor volume. Tumor shrinkage was defined as tumor reduction > 50% of the volume, and tumor progression was defined as a > 25% increase in the volume of the tumor at the last follow-up. Otherwise, the tumors were classified as having no change [15].

Pituitary adenomas bulging into the chiasmatic cistern or beyond were classified as supra-sellar extending (Type A or higher as per Hardy classification) [16]. Adenomas extending beyond the intercarotid/median carotid line laterally were labeled as having cavernous sinus extension (Grade 2 or higher as per Knosp classification) [17]. Those which had eroded the sellar floor and had come to lie in the sphenoid sinus were classified as inferior extending. Pituitary adenomas extending over the planum sphenoidale into the frontal lobe were classified as anterior extending. Posterior growth

was reported when the tumor extended into the interpeduncular cistern and/or prepontine area or beyond. In the follow-up cohort, majority tumors extended into cavernous sinus (42 of 63, 66.7%), followed by suprasellar extension (21 of 63, 33.3%); 7 (11.1%) adenomas were intra-sellar. The mean pre-GKRS volume of NFPAs was 3.1 ± 2.5 cm^3 (Table 2).

GKRS technique

Stereotactic radiosurgery was performed with Leksell® Gamma Knife (Model C till 2016 and Perfexion from 2017 onwards). Leksell® stereotactic frame was applied to patient's head under local scalp anesthesia. The patient was transferred to the magnetic resonance imaging (MRI) room and high-resolution contrast-enhanced axial images of the brain were obtained in the three-dimensional spoiled gradient recalled sequence, and the data was transferred to the gamma knife planning computer via ethernet. The Leksell Gamma Plan® software was used to perform the dose planning (Fig. 1). The goal of GKRS dose planning for NFPA was to achieve a prescribed marginal dose ≥ 10 Gy while keeping the radiation reaching the anterior visual pathway ≤ 8 Gy, and covering the whole tumor within 50% isodose lines. Exposure to the normal gland and pituitary stalk was not always accounted for due to the inconsistency in the clear-cut delineation of the normal structures from the tumor. In the subset of cases with clear delineated stalk, the radiation exposure was kept ≤ 9 Gy.

The median prescription dose delivered to the tumor margin was 13 Gy (range, 8 to 15 Gy), while the maximum dose varied from 16 to 30 Gy, with a median dose of 26 Gy. The prescription isodose was 50% in 59 patients, 40% in 3 patients, and 30% in 1 patient. The median number of isocenters used was 14 (range, 6–31), and the maximum dose to the anterior visual pathway varied from 3.2 to 9 Gy (median 6.4 Gy). (Table 3).

Statistical analysis

Survival analysis was carried out using the Kaplan–Meier technique and compared by using a log-rank test. 5-year progression free survival (PFS) and overall survival (OS) were calculated, along with (GKRS induced) endocrinopathy free survival (EFS), with either the last follow-up or death as the primary endpoints. Possible prognostic factors like patient's age, gender, margin dose, tumor volume etc. were examined using statistical tests (Chi-square; Univariate analysis). Chi-square test with Yates correction was applied to test differences between immunohistochemistry positivity, extra-sellar tumor extension, supra-sellar tumor extension etc., and Mann–Whitney U test was used to compare difference in time after GKRS, between the patients with tumor control and those with
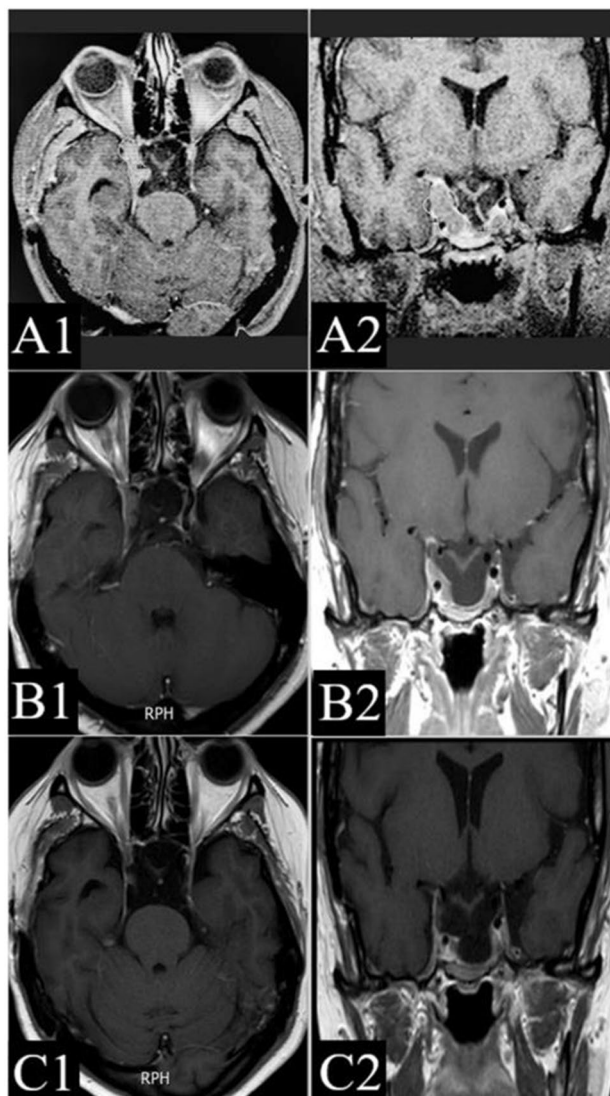

Fig. 1 Serial contrast enhanced MRI Brain images (including GKRS planning) in a case of stable residual NFPA with bilateral (left > right) cavernous sinus extension treated with GKRS. A1-2 GKRS planning MRI images showing contrast enhancing residual lesion in the bilateral (left > right) cavernous region in axial (A1) & coronal (A2) plane. Patient received a margin dose of 13 Gy at 50% isodose (yellow line) through 6 shots. B1-2 Axial (B1)&coronal (B2) fat suppressed contrast images, at 1-year post-GKRS, showing reduction in the residual tumor volume. C1-2 5-year follow-up fat suppressed contrast MRI scan in axial (C1) & coronal plain (C2) showing near complete resolution of the residual tumor in both the cavernous sinuses

tumor progression. Results were considered significant if the P-value was < 0.05. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software, version 23 for Windows®.

Table 3 Radiotherapeutic profile in the follow-up cohort

Parameter	Value
Sessions of GKRS, N	63
Marginal dose in Gy, median (range)	13 (8–15)
Maximum dose in Gy, median (range)	26 (16–30)
Number of isocenters, median (range)	14 (6–31)
Isodose line in %, median (range)	50 (30–50)
Dose to AVP in Gy, median (range)	6.4 (3.2–9)

AVP anterior visual pathway, *GKRS* gamma knife radiosurgery, *SD* standard deviation

Results

Endocrine outcome

In the follow-up cohort, 11 patients already had panhypopituitarism (hypocortisolism, hypothyroidism and hypogonadism) pre-GKRS. Of the 52 patients with residual pituitary hormonal function at the time of GKRS, 25 (48.1%) developed ≥ 1 new pituitary hormone deficiency at median time of 38 months (range, 8–97 months). Only hypocortisolism, hypothyroidism and hypogonadism developed in 4, 7 and 5 patients respectively. Three patients developed hypocortisolism and hypothyroidism, 2 developed hypocortisolism and hypogonadism, and 2 developed hypothyroidism and hypogonadism. Two patients developed panhypopituitarism. Out of 25 patients who did not have any pre-GKRS endocrinopathy, 2 patients developed only hypocortisolism, 4 developed only hypothyroidism, 3 developed hypocortisolism and hypothyroidism, 1 developed hypocortisolism and hypogonadism, and 2 developed panhypopituitarism.

Median time to development of hypocortisolism, hypothyroidism and hypogonadism was 38 months (range, 8–55 months), 45.5 months (range, 12–97 months), and 45 months (range, 21–75 months), respectively. The actuarial risk of developing a new pituitary hormone deficit at 1, 3, 5, 7, and 10 years was 2.5%, 11%, 26.3%, 28% and 29.7% (Table 4). One patient with secondary cortisol deficiency experienced an improvement of adrenal function at 14 months after GKRS, leading to cessation of glucocorticoid replacement.

By Kaplan–Meir survival analysis, 5-year endocrinopathy free survival (EFS) in NFPA post-GKRS was 47.1% (Fig. 2B). Though age ≥ 45 years, female gender, marginal radiation dose of < 13 Gy, and pre-GKRS tumor volume > 5 cm^3 were the parameters that predicted better endocrinopathy free survival, none of these reached statistical significance. (Table 5).

Tumor control

Overall tumor control rate in the follow-up cohort was 87.3% at the last follow-up. Adenoma size decreased in 36 (57.1%) patients and remained stable in 19 (30.2%) patients. The median follow-up time of patients with tumor reduction was 86 months after GKRS (range, 6 to 260 months). Tumor progression was seen in 8 patients (12.7%), and the median follow-up time was 55.5 months after GKRS (range, 6 to

Table 4 Endocrinopathy status in the follow-up cohort

(A) Time to hormone deficiency post-GKRS		
Type of GKRS induced endocrinopathy	No. of patients, N	Time to endocrinopathy in months, median(range)
None	27	
Hypocortisolism	11	38 (8–55)
Hypothyroidism	14	45.5 (12–97)
Hypogonadism	11	45 (21–75)

(B) Hormonal status of patients post-GKRS					
Endocrinopathy (% axes)*	1st year post-GKRS	3rd year post-GKRS	5th year post-GKRS	7th year post-GKRS	10th year post-GKRS
Hypopituitarism (%, out of 118)	3 (2.5)	13 (11)	32 (27.1)	34 (28.8)	36 (30.5)
Hypocortisolism (%, out of 36)	2 (5.6)	5 (13.9)	11 (30.6)	11 (30.6)	11 (30.6)
Hypothyroidism (%, out of 36)	1 (2.8)	5 (13.9)	12 (33.3)	12 (33.3)	14 (39.9)
Hypogonadism (%, out of 46)	0 (0)	3 (6.5)	9 (19.6)	11 (23.9)	11 (23.9)

*Calculated from number of uninvolved pituitary hormone axes pre-GKRS, N = 118

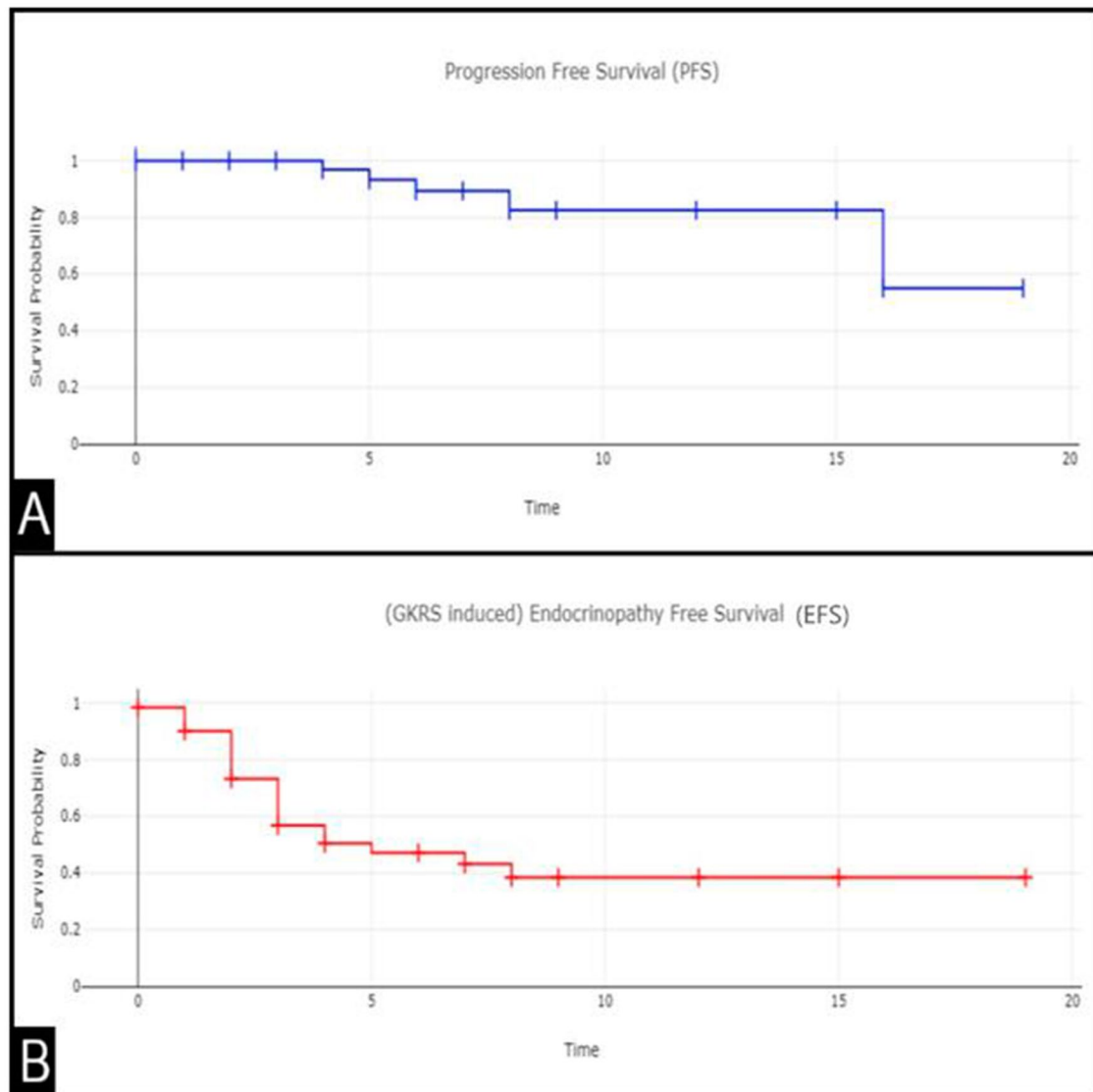*GKRS* gamma knife radiosurgery, *SD* standard deviation

Fig. 2 Kaplan–Meier survival analysis in the follow-up cohort. **A** Kaplan–Meier plots estimating the progression free survival (PFS) in the patients of NFPA who underwent adjunctive GKRS. The 5-year PFS was estimated to be 93.3%. **B** Kaplan–Meier curves estimating the (GKRS induced) endocrinopathy free survival (EFS). The 5-year (GKRS induced) EFS was estimated to be 47.1%

163 months) (Table 6). Of the 8 patients with increase in the tumor size, 5 underwent additional surgical resection, and 1 amongst them underwent repeat GKRS post-resurgery after 163 months of initial GKRS. (Table 7).

By Kaplan-Meir survival analysis, the 5-year progression free survival (PFS) and overall survival (OS) for patients after GKRS were 93.3% and 100%, respectively (Fig. 2A). On subgroup analysis, the PFS appeared higher for patients aged < 45 years, female patients, patients receiving marginal radiation dose ≥ 13 Gy, and patients with tumor volume ≤ 5 cm^3, but none were statistically significant (Table 5).

There was no difference between the tumors that were controlled after GKRS (N = 55), from those that progressed (N = 8) when compared with respect to immunohistochemistry (IHC) staining for any of LH, FSH, TSH, ACTH, GH or prolactin (77.4% vs 87.5%, P = 0.85), gonadotroph (LH/FSH) positivity on IHC (43.4% vs 37.5%, P = 0.945), extra-sellar extension (89.1% vs 87.5%, P = 0.643), supra-sellar extension (30.9% vs 50%, P = 0.504) and cavernous sinus extension (69.1% vs 50%, P = 0.504). Median time to GKRS after last surgery did not significantly differ between the controlled and the progressed groups (307 vs 259 days, P = 0.726).

Table 5 Summary of the Kaplan–Meier survival analysis in the follow-up cohort

Parameter	Percentage(%)	Better Outcome predictor	P-value (log rank test)
5-year Overall Survival	100	–	–
5-year (GKRS induced) EFS	47.1	–	–
5-year (GKRS induced) EFS & Age		≥ 45 years	0.632
< 45 years	40.3		
≥ 45 years	52.7		
5-year (GKRS induced) EFS & Gender		Female	0.392
Male	40.9		
Female	63.3		
5-year (GKRS induced) EFS & Margin dose		< 13 Gy	0.781
< 13 Gy	51.3		
≥ 13 Gy	45		
5-year (GKRS induced) EFS & Volume		> 5 cm^3	0.357
≤ 5 cm^3	36.6		
> 5 cm^3	48.1		
5-year PFS	93.3	–	–
5-year PFS & Age		< 45 years	0.406
< 45 years	93.8		
≥ 45 years	92.3		
5-year PFS & Sex		Female	0.972
Male	91.3		
Female	92.3		
5-year PFS & Margin dose		≥ 13 Gy	0.462
< 13 Gy	83.9		
≥ 13 Gy	100		
5-year PFS & Volume		≤ 5 cm^3	0.522
≤ 5 cm^3	100		
> 5 cm^3	91.8		

EFS endocrinopathy free survival, *PFS* progression free survival

Table 6 Tumor volume changes in the follow-up cohort

Outcome	Pre-GKRS volume in cm^3, mean ± SD	Post-GKRS volume in cm^3, mean ± SD	Time to outcome in months, median (range)
Tumor volume shrinkage (36 of 63, 57.1%)	3.1 ± 1.9	1.3 ± 0.9	86 (6–260)
No change in tumor volume (19 of 63, 30.2%)	3.1 ± 2.7	2.6 ± 1.9	28 (6–86)
Tumor volume progression (8 of 63, 12.7%)	2.9 ± 3.1	4.3 ± 4.1	55.5 (6–163)
Total (N = 63)	3.1 ± 2.5	2.4 ± 1.9	41.5 (6–260)

GKRS gamma knife radiosurgery, *SD* standard deviation

Complications

The complications noticed in the follow-up cohort are listed in Table 7. One patient, who had received a maximum radiation dose of 28 Gy, developed severe headache on day 2 post-GKRS. He improved over the next 2 days with only symptomatic management. Another patient had worsening of vision and deterioration of visual fields on follow-up at 16 months, and on MRI was diagnosed to have developed bilateral optic atrophy. She had received a maximum radiation dose of 24 Gy, and 5.2 Gy to the anterior visual pathway.

Table 7 Complications of gamma knife Radiosurgery & additional therapy received in the follow-up cohort

Complication	Number of patients
Worsened headache, N(%)	1 (1.6)
Optic Atrophy, N(%)	1 (1.6)
CVA, N(%)	1 (1.6)
Additional therapy required, N(%)	
TSS	3 (4.8)
TCS + TSS	1 (1.6)
TSS + TSS + Redo-GKRS	1 (1.6)

CN cranial nerve, *CVA* cerebrovascular accident, *GKRS* gamma knife radiosurgery, *TCS* trans-cranial surgery, *TSS* Trans-sphenoidal surgery

A male patient with posterior extension of NFPA, who had undergone GKRS at 71 years of age, had left cerebellar infarct after 60 months of GKRS. His tumor size had remained stable over the period (3.3–2.8 cm^3). He had received a maximum radiation dose of 26 Gy, with a marginal dose of 13 Gy. He had not received any additional therapy after GKRS.

No patient experienced any diplopia, cranial nerve palsy or radiation necrosis as immediate or short-term complication. None of the patients had hydrocephalus or second neoplasm till last follow-up.

Discussion

Though surgical adenomectomy remains the treatment of choice for NFPA, the chance for residual or recurrent disease remains high. Adjunctive treatment modalities, like GKRS, have a major role to play in managing such residual or recurrent NFPA, and averting the need for resurgery. Long-term tumor control rates of NFPA patients are shown to be higher with GKRS in comparison to conventional fractionated radiotherapy [13, 18]. The evidence-based knowledge about the GKRS outcomes in NFPA is limited and needs expanding, especially the endocrine outcome. We retrospectively analysed the long-term endocrine and imaging outcome and the influencing factors in our study group. This is the first such report in the south Asian region in treating NFPA with adjunctive GKRS.

Endocrine outcome

Delayed hypopituitarism is the single most important complication seen in the post-GKRS NFPA patients. There is a wide spectrum of reported adverse endocrine outcomes in the current literature from large cohorts, ranging from 4 to 32% [5, 9, 11, 12, 14, 19–24]. Hayashi et al. reported

0% new hypopituitarism in patients who received GKRS for NFPA in cavernous sinus location only [25]. Incidence of GKRS induced hypopituitarism was comparatively higher (25 of 63, 39.7%) in our study, with ≥ 1 new pituitary hormone deficiency developing at median time of 38 months. 2 patients developed panhypopituitarism. In our study, deficiency of thyroid axis (22.2%) was most commonly seen, followed by adrenal and gonadal axes (17.5% each). Liscak et al. and Kara et al. reported hypocortisolism being the most common, followed by hypothyroidism and hypogonadism [24, 26]; while gonadal, thyroid and adrenal axes were involved in 9%, 7% and 5% patients in the study by Sun et al. [20], in NFPA patents after GKRS. These differences in hormonal axes involvement may be due to small number of actual outcomes.

We observed better 5-year (GKRS induced) EFS rates in patients aged ≥ 45 years (52.7% vs 40.3%) and female patients (63.3% vs 40.9%). Similarly, patients with lesser median marginal dose of radiation (< 13 Gy) had a better EFS (51.3% vs 45%). Leenstra et al. in their study of adjuvant GKRS in NFPA noted 30% pituitary deficits for doses < 15 Gy, compared with 45% who received a mean dose > 15 Gy [27]. In our study, patients with tumor volume of > 5 cm^3 had a better EFS (48.1% vs 36.6%). This reported relationship of the tumor volume and endocrinopathy status is in disagreement with the findings of a systematic review and meta-analysis published by Pollock BE et al. [12]. Another large cohort by Kara et al. also made observations in agreement with that of Pollock et al.'s review [26]. In our cohort, the patients with a tumor volume of > 5 cm^3 (N = 10) had received significantly lesser maximum dose (23.6 ± 3.8 vs 26.3 ± 2.4 Gy, P = 0.005) and marginal dose (11.1 ± 1.9 vs 13.1 ± 1.2, P < 0.001) of radiation as compared to patients with adenoma volume ≤ 5cm^3 (N = 53), which may explain our observation regarding tumor volume and endocrinopathy status.

Imaging outcome

Tumor control was seen in 87.3% patients, which has been consistent with other studies reporting 85 to 91% tumor control with GKRS in NFPA [9, 11, 19, 20, 22, 28]. A few studies have reported 95 to 100% tumor control post-GKRS [21, 23–25]. Long term radiologic outcomes have been excellent with all large cohorts reporting 5-year PFS in excess of 90% [5, 9, 11, 12, 14, 19–23, 27, 28], and our results of 5-year PFS of 93.3% are in accordance with them. The 5-year PFS was better for patients aged < 45 years, female patients, patients receiving marginal radiation dose ≥ 13 Gy, and patients with tumor volume ≤ 5 cm^3. Park et al. and Narayan et al. reported worse control in tumors > 5 cm^3 [9, 11], while Sheehan et al. observed poorer GKRS outcomes in tumors with suprasellar extensions [5]. Though minimal

effective dose of radiation for tumor control remains debatable, Gopalan et al. observed that NFPA inclined to progress with GKRS doses < 12 Gy [29], while Mingione et al. reported that doses > 20 Gy did not significantly better tumor control rates [30]. A recent meta-analysis studying GKRS outcomes in pituitary adenomas by Albano et al. did not find significant differences in tumor control rates with increasing prescription doses [18]. There is conflicting data regarding tumor control with early GKRS (within 6 months) after surgery, with studies by Kara et al. and Promeraniec et al. observing a significantly lower rate of NFPA progression [26, 31], while Sadik et al. detected no such significant difference in tumor progression with the timing of GKRS [21]. In their systematic review, Albano et al. recommend early radiosurgical therapy in patients who undergo adenomectomy and have a clear residual mass [18].

Grave complications

Several gamma knife centers have reported GKRS to be a safe treatment in patients with NFPA. Many studies have reported 0% incidence of optic neuropathy after GKRS for NFPA [11, 12, 14, 21, 24, 28], others have reported development of optic neuropathy in 1 to 4% patients [9, 19, 20, 22, 23], while Sheehan et al. had an incidence of 7% in their study [5]. In our study, 1 patient (1.6%) developed optic atrophy after GKRS. The optic chiasm typically lies 10 mm above the pituitary gland, and in 80% of the population rests immediately above the sella. It may rest above tuberculum sellae in 10% (having short optic nerves and long optic tracts), and above dorsum sellae in the remaining 10% of the population (having long optic nerves and short optic tracts) [32]. Therefore, accurate stereotactic localization and headframe placement is critically important not only for precise delivery of ionizing radiation to the adenoma, but also to prevent inadvertent exposure of radiation to the anterior visual pathway and other structures at risk.

In our cohort, a diabetic and hypertensive male patient with posterior extension of NFPA, who had undergone GKRS at 71 years of age, had cerebellar infarction after 60 months of GKRS. He had received a maximum radiation dose of 26 Gy, with a marginal dose of 13 Gy. Van Westrhenen A et al. in their systemic review of ischemic stroke after radiation therapy for pituitary adenomas reported incidence ranging from 0 to 11.6%, with no reports of ischemic stroke in patients receiving stereotactic radiosurgery [33]. Irradiation to the arteries in the field of radiation (cavernous segment of internal carotid artery in parasellar extending adenomas, or circle of Willis in suprasellar extending adenomas) may predispose them to accelerated atherosclerosis, thereby increasing the risk of ischemic infarction. There is no data to suggest if occurrence of stroke is prescription dose dependent. However, Shin et al.

recommend < 30 Gy dose restriction to cavernous part of internal carotid artery to prevent postradiosurgery stenosis [34]. More recent study has however observed that there are no increased anatomical brain abnormalities (cerebral atrophy, brain infarctions, abnormalities of the temporal lobes and hippocampi) in patients receiving radiotherapy for NFPA, as compared to surgery alone [35]. Another study reported pre-existing coronary artery disease, peripheral artery disease, and hypertension as the primary risk factors for occurrence of stroke in patients with pituitary adenomas, irrespective of treatment with radiation therapy [36]. In our study, the patient who suffered from cerebellar infarction post-GKRS, likely represents an independent event unrelated to radiotherapy.

In patients with NFPA, post-GKRS new cranial nerve palsies have been reported in a few studies, with incidence varying from 1.6 to 9% [5, 9, 19, 22]. Only one study reported hydrocephalus (1.7%, 1 patient) [22], while none of the referenced studies have reported radiation necrosis or secondary tumors in patients receiving GKRS for NFPA. No patient developed cranial nerve palsy, radiation necrosis, hydrocephalus or second neoplasm in our cohort.

Limitations

Relatively small sample size and questionable representativeness of the study population act as limitations for the sub-group analysis. Though Pomeraniec et al. reported that the dose ratio to pituitary stalk over the normal gland of ≥ 0.8 was an independent indicator for GKRS induced endocrinopathy, a similar analysis was not possible in our retrospective analysis [37]. We had other significant differences in few of our findings with that of the available literature. However, it is important to highlight that such comparisons between retrospective studies are limited by differences in the patient/tumor/treatment characteristics that can significantly affect outcomes. No statistically significant results regarding parameters affecting outcomes were obtained. The inability to standardize MRI slice thickness and magnet strength during the follow-up visits adds to the limitations of our study.

Conclusion

Adjunctive GKRS in NFPA has an excellent 5-year progression free survival of 93.3%. Risk of GKRS induced endocrinopathy exists, and we report a 5-year (GKRS induced) endocrinopathy free survival of 47.1%. GKRS offers a high rate of tumor control, with satisfactory long-term preservation of hormone functions in patients with NFPA. GKRS is an effective and safe adjunctive treatment modality for patients with NFPA.

Declarations

Conflict of interest The authors declare that they have no known competing financial interest or personal relationships that could have appeared to influence the work reported in this paper.

Ethical approval Ethical approval was waived by the local Ethics Committee of P. D. Hinduja Hospital in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

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