World Neurosurgery: X 22 (2024) 100327

Contents lists available at ScienceDirect

World Neurosurgery: X

journal homepage: www.journals.elsevier.com/world-neurosurgery-x

Should post-operative stereotactic radiosurgery be the standard of care in Craniopharyngioma patients?

Saurabh Gupta, Deepak Agrawal *, Shweta Kedia, Shashank Sharad Kale

Department of Neurosurgery, All India Institute of Medical Sciences, New Delhi, India

ARTICLE INFO

Keywords:
Craniopharyngioma
Gamma knife
Radiosurgery
Survival
Stereotactic

1. Introduction

Craniopharyngiomas are locally aggressive, histologically benign (WHO Grade I) intracranial neoplasms, most commonly occurring during childhood. They are extra-axial epithelial tumors that arise from squamous epithelial remnants of Rathke's pouch, near the pituitary gland. Craniopharyngiomas have a bimodal distribution by age, with peak incidence being in childhood (0–19 years) and in older adults (40–79 years). They constitute 5–13% of all paediatric brain tumors, and are the most common non-glial tumors of childhood. The clinical presentation results from compression of surrounding neurovascular structures. The common symptoms include diminution of vision (~50%), headache (60–75%), diplopia, short stature, delayed sexual maturation, diabetes insipidus, obesity secondary to compression of the optic chiasm, the third/sixth cranial nerves, the pituitary stalk, or the hypothalamus. Hydrocephalus is also common secondary to compression of foramen on Monroe.

Surgical excision remains the gold standard for management of craniopharyngiomas. However, the vicinity of the tumor to the aforementioned neurovascular structures often makes complete resection challenging. Pituitary deficiencies and hypothalamic disturbances have been reported in 50–92% of patients undergoing complete tumor resection. Despite advances in microsurgical and endoscopic techniques, significant operative morbidity and mortality rates continue to pose formidable challenges to long-term remission from craniopharyngiomas. Moreover, the locally aggressive nature of these tumors can hinder the complete visualisation of tumor from the chosen surgical corridor, leading the surgeon to a false impression of complete excision.

It is seen that subtotal resection combined with radiation therapy produces similar, if not better survival than gross total excision of craniopharyngioma. This approach has led to 5-year progression-free survival (PFS) rates exceeding 90%.[1–3] At the same time, it reduces the visual, cognitive and endocrine morbidities associated with the attempted complete resection of the tumor. Gamma knife radiosurgery (GKRS) allows the radiation field to be closely tailored to the tumor volume, minimizing the radiation dose to surrounding hypothalamic and visual structures. This also permits a more liberal use of radiation therapy in the post-operative period, and reduces the need of complete tumor excision by the neurosurgeon at the cost of post-operative functional impairment. Over the past two decades, few studies have been conducted to assess the efficacy and safety of stereotactic radiosurgery for residual and recurrent craniopharyngiomas. Most of them have yielded optimistic results with 5-year tumor control rates approaching up to 85%, and with acceptable complication rates.[3–11] However, there is no consensus on treating residual tumors with GKRS.

This study assesses the progression free survival, visual and endocrine outcome of all consecutive patients who received gamma knife therapy for residual and recurrent craniopharyngiomas at our institution. It compares these outcomes with all surgically treated craniopharyngioma patients who did not receive any adjuvant radiation treatment.

* Corresponding author. Department of Neurosurgery & Gamma Knife, All India Institute of Medical Sciences, New Delhi, India.
E-mail addresses: drsaurabh3009@gmail.com (S. Gupta), drdeepak@gmail.com (D. Agrawal), drshwetakedia@gmail.com (S. Kedia), sskale67@gmail.com (S.S. Kale).

https://doi.org/10.1016/j.wnsx.2024.100327
Received 18 April 2023; Accepted 21 February 2024
Available online 25 February 2024

2. Methods

Patient Population A total of 36 patients received GKRS for residual or recurrent craniopharyngioma between 2011 and 2019 at the All India Institute of Medical Sciences, New Delhi, India. Of these, one patient was lost to follow-up, and was excluded from the study. So, all 35 patients under follow-up were analysed in the GKRS group.

In the two year period from 2018 to 2019, a total of 58 patients underwent surgery for craniopharyngioma at our institute. 44 of these patients had not received any post-operative radiation therapy. This comprised the control group. After obtaining approval from the Institute Ethics Committee, all of the 79 patients (35 GKRS group, and 44 control group) were included in this observational study. The medical records of these patients were retrieved from our hospital database for the purpose of this study, and patients were followed up clinically.

As all patients had a >12 month follow-up, all patients were included in the study.

Gamma Knife Treatment**:** Radiosurgery was administered using Leksell Gamma Knife Perfexion (Elekta Instrument AB, Stockholm, Sweden). The planning team included a neurosurgeon, a medical physicist and a radiation oncologist, and was based on 1 mm thin, gadolinium contrast-enhanced magnetic resonance imaging acquired on the day of treatment. A prescription dose of 12 Gy was applied to the tumor margin at the 50% isodose line (Range 11–15 Gy), and it was ensured that the optic apparatus did not receive a dose of more than 8Gy.

Follow Up: As per the department's protocol, patients undergo contrast enhanced magnetic resonance imaging (CE-MRI) brain every 12–18 months following GKRS to assess response, and plan further management in case of recurrence. The GKRS patients on the follow-up visits undergo clinical, biochemical, ophthalmological and endocrinological assessment, the details of which are as follows:

a) Radiological Assessment:

On the basis of CE-MRI imaging done at follow up, the tumor volume was calculated using Leksell GammaPlan® software. Radiological response was divided into four groups based on the Response Assessment in Neuro-Oncology (RANO) criteria.[12]

- Complete Response (disappearance of lesion on CE-MRI),
- Partial Response (>50% reduction in volume),
- Stable disease (less than 25 % increase, to a reduction of <50%), and
- Progressive disease (More than 25% increase in volume)

b) Visual Assessment:

The visual assessment comprised of visual acuity and visual field assessment for all patients who received GKRS by an ophthalmologist. WHO criteria[13] for vision was used:

- "Normal" vision: Visual acuity equal to or better than 6/18.
- "Impaired" vision: Visual acuity between 6/18 and 3/60.
- "Blindness": For visual acuity of <3/60, or finger counting at less than 3 m.

c) Endocrinological Assessment:

The patients were followed up annually at our institute's endocrinology department, with a complete blood workup (T3, T4, TSH, cortisol, FSH, LH, GH, GnRH, features of DI). Hormone therapy was modified by them based on the reports.

Survival Analysis: Kaplan–Meier analysis and Log-rank tests were used to compare the overall survival (OS), and Progression free survival (PFS) between the two groups using IBM® SPSS® Statistics ver.23. Multivariate analysis was done using Cox progressional-hazard method to identify prognostic factors affecting survival in craniopharyngioma patients.

3. Results

Patient Demographics: The GKRS group included 35 cases, with a median age of 21 years (Range: 6–55 years), and had twenty-one (60%) adults (age>18 years), and fourteen (40%) pediatric patients (age<18 years). It included ten females (28.6%), and twenty-five males (71.4%). This group had a mean follow-up of 62 months (range 24–117.6 months). (Table 1).

The group which did not receive any radiation treatment had 44 cases, with a median age of 16 years (range 3–51 years), and included nineteen adults (43.2%) and twenty-five pediatric (56.8%) patients. Females constituted 20.5% (n = 9), and males made up 79.5% (n = 35) of the cases. The median follow-up in this group was 47.4 months (range 12.7–61.7 months). No significant difference ($p > 0.05$) was found in the age and sex of the two groups.

Treatment received: All patients who received GKRS had previously been operated, and were histologically proven cases of craniopharyngioma. Twenty-seven (77.1%) of the thirty-five patients had undergone a single transcranial surgery for tumor excision. Seven patients (20%) had history of multiple transcranial surgeries for tumor excision prior to receiving gamma knife treatment. One (2.9%) patient had undergone tumor excision twice via endoscopic trans-sphenoidal route. Sixteen patients (45.7%) received radiation within 6 months of surgery, while nineteen patients (54.3%) received it beyond 6 months of surgery.

Of the 44 patients who did not receive any radiation treatment, three (6.8%) underwent surgery via endoscopic endonasal route, while the remaining forty-one cases (93.2%) had tumor removed via transcranial (pterional, bifrontal or frontotemporo-orbitozygomatic) approaches. Gross total excision was achieved in 29 patients (65.9%).

3.1. Gamma knife radiosurgery (GKRS) group

Of the thirty five cases included in this group, 16 sessions (45.7%) were for solid tumors, while 19 sessions (54.3%) were for tumors with both solid and cystic components. The tumor volume ranged from 80.6 to 13,910 mm^3 (mean 3258 mm^3, median 1840 mm^3).

3.1.1. Baseline vision

Nine patients (25.7%) had normal baseline vision (WHO criteria) in both eyes prior to gamma knife treatment. One patient (2.8%) was blind in both eyes. Seven Patients (20%) had a visual field defect at the time of presentation for gamma knife treatment.

3.2. Baseline endocrinological evaluation

At the time of receiving GKRS, 13 patients (37.1%) were on thyroxine supplementation, and 13 patients (37.1%) were on corticosteroid supplementation, and five patients (13.51%) were on vasopressin supplementation for diabetes insipidus.

3.3. Treatment parameters

The radiation dose for GKRS ranged from 11 to 15 Gy at 50% isodose. 31 sessions involved use of 12 Gy at 50% isodose. 3 sessions involved use of 11 Gy at 50% isodose, due to proximity to optic apparatus. One patient had received 15Gy based on the treating team's preference.

3.4. Ophthalmological outcome

Two patients reported improvement in visual acuity in both eyes, and three patients reported improved visual field post gamma knife therapy.

One patient (Case E) had worsened bilateral visual acuity and visual field, and was found to have progression of tumor, for which surgical decompression was required. The vision did not improve after surgery.

Table 1
Demographics and tumor characteristics.

	n	Mean	Std. Deviation	Median	Q1	Q3	IQR
GKRS Group							
Age (yrs)	35	23.91	13.64	21.0	14.0	34.0	20.0
Males	25						
Follow Up (Months)	35	62.01	26.01	60.1	37.7	82.9	45.2
Interval between Surgery and Radiation (months)	35	18.82	33.59	6.5	4	16.8	12.8
Dose	35	12.00	0.59	12	12	12	.0
Tumor Solid	16						
Solid-Cystic	19						
Subtype							
Adamantinomatous	10						
Papillary	3						
Unspecified	22						
Control Group							
Age (yrs)	44	18.45	12.600	15.5	9	25.75	16.8
Males	35						
Follow Up (Months)	44	42.8	14.458	47.4	34.9	53.10	18.2
Subtype							
Adamantinomatous	33						
Papillary	2						
Unspecified	9						
Tumor Solid	0						
SolidCystic	38						
Cystic	6						

IQR: Interquartile range (Q3-Q1).

3.5. Radiological response

Radiological response has been divided into four groups based on the Response Assessment in Neuro Oncology (RANO)[12] criteria **(Table 2).**

32 of the 35 cases (91.4%) resulted in non-progression (i.e. stable disease, and partial response) of the tumor, with 9 sessions (25.7%) showing more than 50% reduction in tumor size.

Of the three patients (8.6%) who had progressive disease, one patient (Case M) had an increase noted at 31 months, but the disease was stable on further follow ups (total 66.5 months), and no surgical intervention was performed. He had no visual or endocrine deterioration and is currently doing well.

One patient (Case E) with progression, had a recurrence 30 months after gamma knife (scan done at 16 months showed stable disease), and presented with worsening vision in both eyes. He required re-do surgery for excision of the tumor at our institution. The patient had multiple recurrences, requiring three more surgical interventions over the next 4 years. The patient expired due to disease progression 96.8 months after the gamma knife session.

The third patient's (Case O) progression was noted in the follow-up scan done at 12 months. He received repeat gamma knife therapy to the solid component of the tumor, and underwent surgical decompression of cyst with ommaya placement and interferon therapy. At the time of his last follow up, scan done at 43 months post GKRS shows stable disease, and the patient is doing well.

Univariate analysis was done to analyze the radiological response in GKRS based on age, sex, mean marginal dose, interval between gamma knife and surgery, and the type of tumor. No statistically significant association was found between these factors with radiological response.

3.6. Endocrine outcome

On follow up endocrinological evaluation, three patients (8.6%) were newly diagnosed with hypothyroidism, and two patients (5.7%) required an increased replacement dose of thyroxine. Also, three patients (23.1%) were tapered off thyroxine on follow up. Corticosteroid supplementation dose reduced for 4 patients post gamma knife therapy, while 3 patients (23.1%) required increase in maintenance dose of corticosteroids. Five patients (14.2%) were newly diagnosed with hypocortisolism on follow up. Diabetes insipidus improved in one patient (33.3%) following gamma knife therapy, and no new onset DI was observed in any of the patients.

3.7. Complications associated with gamma knife

No local complications associated with radiation therapy were observed in any of the patients. None of the patients developed any worsening of visual field or any new cranial nerve deficits. However, at the time of last follow up, 5 patients (14.2%) without tumor progression, with previously normal pituitary functions, had been started on maintenance doses of hormone supplements by the endocrinology team based on their assessment.

Progression- Free Survival (Fig. 1):

The actuarial progression free survival (PFS) rates using Kaplan–Meir plots were found to be 100%, 92.3% and 92.3 % at 1, 3 and 5-years respectively for GKRS group.

Table 2
Radiological response based on Response Assessment in Neuro Oncology (RANO) criteria.

Group	GKRS			No GKRS		
	No. of pts	Percent	Mean Follow-up (months)	No. of pts	Percent	Mean Follow-up (months)
	(n = 35)			(n = 44)		
Complete Response (disappearance of lesion)	0	0	NA	11	25%	48.5
Partial response (>50% reduction)	9	25.71%	64.1	24	54.55%	31.7
Stable Disease (<25% increase to 50% reduction in size)	23	65.71%	63.3	0	0	NA
Progressive Disease (>25% increase)	3	8.57%	At increase: 24.9 Total: 84.4	9	20.45%	At increase: 16.9 Total: 47.4
	35			**44**		

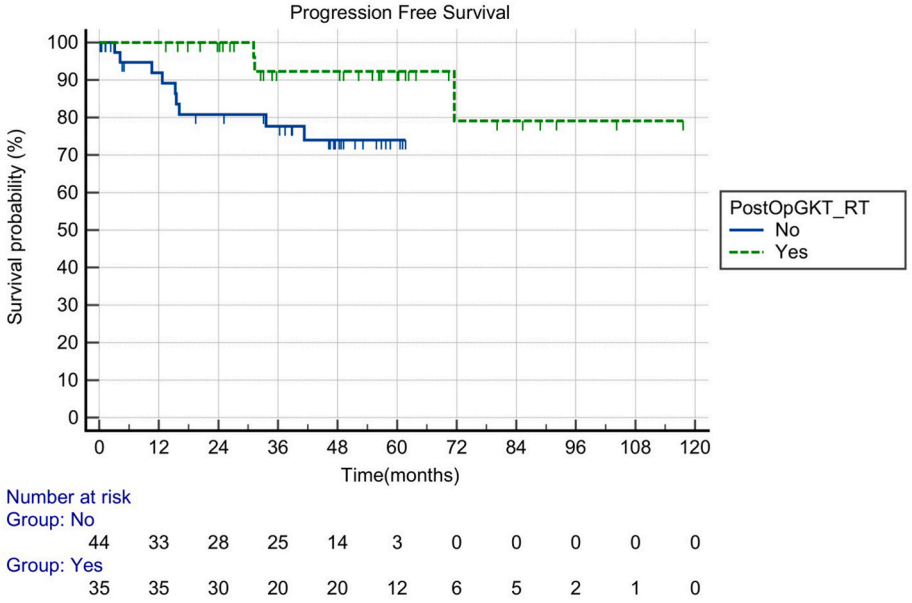

Fig. 1. Kaplan-Meier graph showing Progression Free Survival (PFS) of patients who received GKRS (Green, dotted), vs patients who did not receive GKRS (Blue).

Within the GKRS group, no statistically significant difference was noted between progression free survival based on age of the patient, tumor type (solid vs. solid-cystic), tumor size, duration between surgery and gamma knife, or prescription dose administered to the tumor (**Table 3**).

Overall Survival (Fig. 2):

Two patients (5.7%) had mortality due to progression of the tumor. Two patients expired in the follow-up period due to unrelated causes. The 1, 3 and 5-year overall survival (OS) rates in GKRS group were noted to be 100%, 97.1% and 97.1%, respectively. No statistically significant difference was seen in of overall survival based on age of the patient, tumor type (solid vs. solid-cystic), tumor size, duration between surgery and gamma knife, or prescription dose administered to the tumor (**Table 3**).

3.8. Group not receiving post-operative GKRS

58 patients were operated for craniopharyngioma between January 2018 and December 2019. Of these, 44 patients did not receive any radiation therapy (GKRS or RT) post-surgery, and were analyzed. The median follow up in this group was 47.4 months (range 12.7–61.7 months). Gross total excision (GTE) was achieved in 29 patients (65.9%).

In the fifteen cases (34.1%) with NTE, one perioperative mortality (6.6%) was observed. Seven patients (42.4%) required surgical intervention for residual disease. Five patients (33.3%) expired due to disease progression in the follow-up period, leading to a total 40% mortality (n = 6 of 15) in cases that underwent NTE. Perioperative mortality was seen in 4 (13.8%) of 29 patients who underwent gross total excision (GTE) of the tumor. One mortality (3.4%) was reported in the follow up period of these patients.

Radiological Response in surgery-alone group (Table 1):

At the time of last follow-up, 35 of 44 (79.55%) patients had non-progression (i.e stable disease, partial response and complete response). 9 patients had progressive disease.

The 1 and 3 year progression-free survival (PFS) was found to be

Table 3
Cox proportional hazards analysis for progression free survival, and overall survival.

Factor	Cox analysis for progression				Cox Analysis for survival			
	95.0% CI for HR				95.0% CI for HR			
	p-value	Hazards Ratio	Lower	Upper	*p*-value	Hazards Ratio	Lower	Upper
All cases (n = 79)								
Age	0.64	0.985	.927	1.05	0.04	1.042	1.001	1.085
Sex (Male)	0.12	2.701	.778	9.38	0.31	1.823	0.569	5.839
GTE/NTE	0.29	0.431	.089	2.08	0.38	1.725	0.508	5.853
PostOpGKRS	0.20	0.256	.032	2.06	0.003[a]	0.055	0.008	0.363
Tumor Type (Solid)	0.90	53.937	.000	2.59E+89	0.99	57.089	0.000	4.24E+91
GKRS Group (n = 35)								
Sex	.76	1E+20	.000	3.01E+146	0.81	29010.047	0.000	5.53E+41
Age	.63	.02	.000	149895.93	0.94	0.845	0.012	59.126
Redo Sx before GKRS	.97	.12	.000	9.65E+45	0.89	0.001	0.000	7.04E+41
Dose (Gy)	.74	3E+12	.000	3.26E+85	0.92	0.186	0.000	4.88E+12
Time between Sx and radiation	.95	.00	.000	7.71E+80	0.76	1.36E+05	0.000	4.11E+37
Tumor Type (Solid)	.61	9E+51	.000	3.94E+252	0.95	5.694	0.000	1.18E+26
Tumor Volume	.85	1.00	.990	1.01	0.88	1.001	0.983	1.020

CI = Confidence Interval.
HR = Hazards Ratio.
[a] $p < 0.05$ significant.

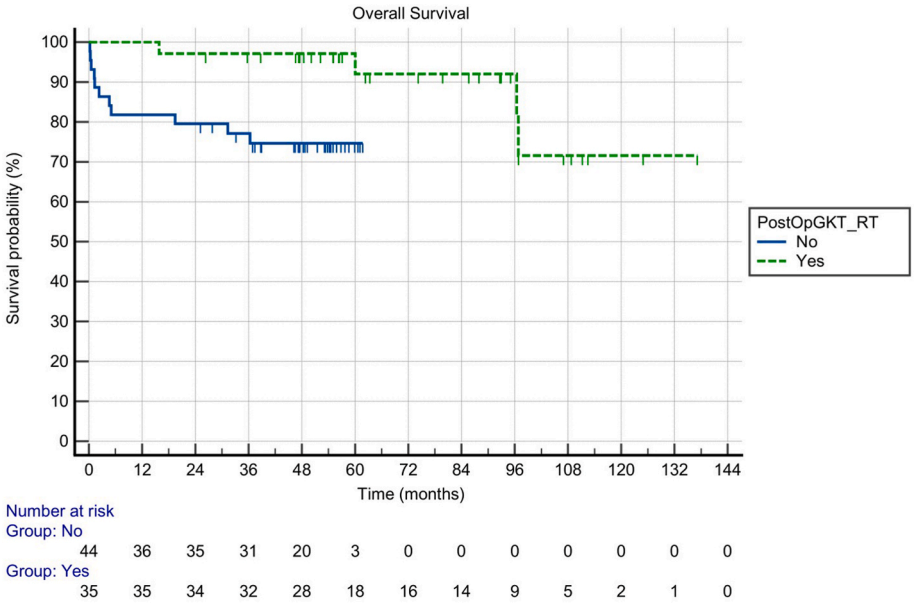

Fig. 2. Kaplan-Meier graph showing Overall Survival of patients who received GKRS (Green, dashed), vs. patients who did not receive adjuvant radiosurgery (Blue, solid).

92.3% and 77.7% respectively for the group that did not receive any post-operative radiation therapy. The overall survival (OS) for these patients at 1 and 3-years was 81.8% and 77.1% respectively.

A subgroup analysis was done to compare the cases who had undergone redo-surgery alone for residual disease (n = 7), vs. cases that had undergone redo surgery for residual disease before receiving GKRS (n = 8). No statistically significant difference in PFS and OS was found between the two small subgroups.

3.9. Survival Analysis

Kaplan–Meier analysis and Log rank tests showed significantly better progression free survival (3-year PFS of 92.3% vs. 77.7%, $p = 0.03$), and overall survival (3-year OS of 97.1% vs. 74.6%, $p = 0.009$) in the group receiving radiation treatment (GKRS).

Cox proportional hazard analysis of the 79 craniopharyngioma patients included in the study revealed post-operative GKRS (HR = .055, 95% CI = .008–.363) to be an independent prognostic factor for overall survival (OS) in craniopharyngioma patients (Table 3).

3.10. Illustrative cases

Case C: A 30-year old male patient presented with complaints of gradually worsening vision in both eyes. His endocrine evaluation revealed hypocortisolism and hypothyroidism. Radiology was suggestive of craniopharyngioma, and he was operated. Post-op imaging revealed residual tumor, and he was planned for gamma knife. At the time of GKRS, he had a blind right eye and a vision of 6/60 in left eye. The tumor control was good, and at a follow up of 117 months, the tumor has shrunk by more than 40%. The patient is same neurologically, and endocrine function has improved (Fig. 3).

3.11. Case K

A 37-year old man, twice previously operated via transcranial route for craniopharyngioma, was planned for gamma knife therapy for the small residual tumor. The treatment was administered six months after the last surgery, with a dose of 12Gy at 50% isodose line. At the time of gamma knife, the vision was intact in the right eye (left eye congenitally absent). The patient had a good response, with a more than 90% reduction in tumor volume at a follow up of 70.4 months. The endocrine function improved post gamma knife, and there was no deterioration in vision. (Fig. 4).

4. Discussion

The optimal management strategy for craniopharyngiomas requires a multidisciplinary approach. Even though surgical excision remains the goal standard, complete resection has a potential to cause untoward damage to adjacent vital structures, the most important ones being the hypothalamus, pituitary stalk and the optical chiasm. Complete excision may be hindered by the adherence to hypothalamus, presence of thick

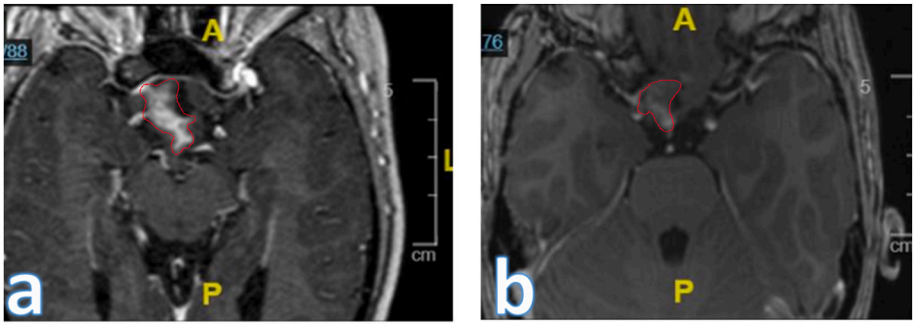

Fig. 3. Illustrative Case (Case C): a) PreGKRS ; b) Follow up MRI at 117 months shows significantly reduced tumor size.

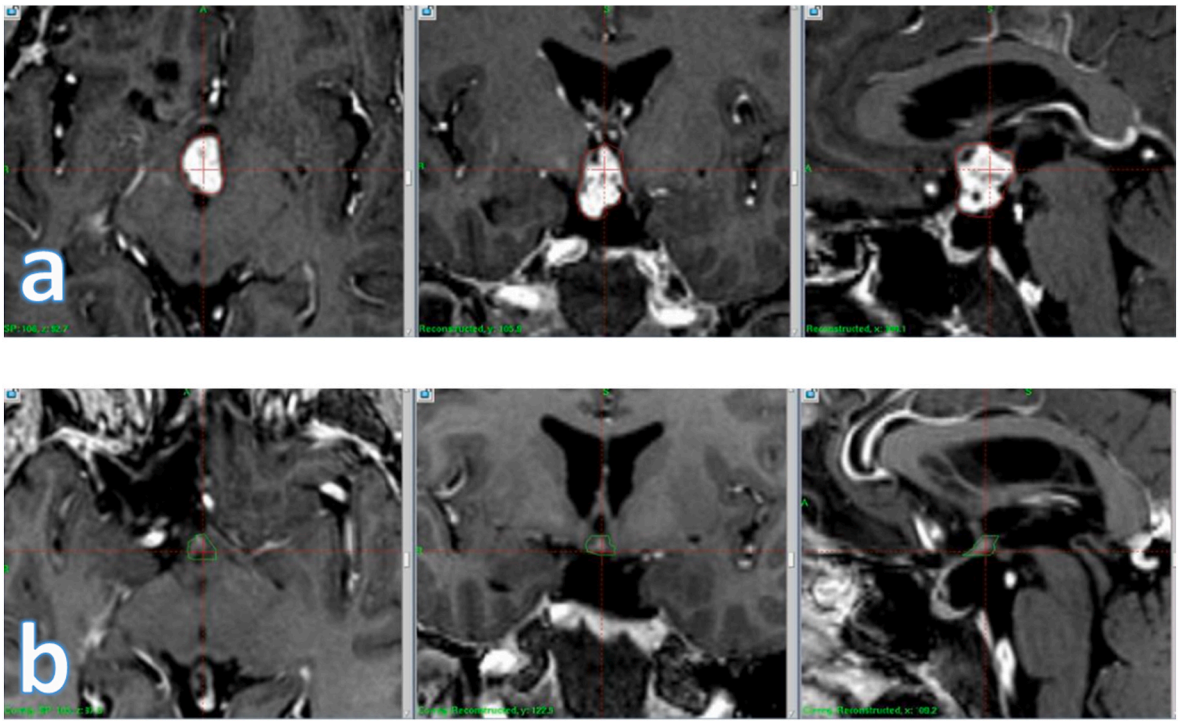

Fig. 4. Illustrative Case (Case K): a) PreGKRS lesion ; b) At 70.4 months post GKRS, more than 90% reduction in tumor volume.

calcifications, or non-visualization of complete tumor by a single approach.

It is to be noted that the surgeon's impression of gross total resection may not be accurate, and it has been reported that 18–26% of cases undergoing complete resection show remnants on post-operative imaging.[14] In our study, four of twenty-nine patients (13.7%) who underwent complete resection had evidence of residual tumor. Tomita and Bowman[15] reported a 5-year recurrence rate of 33% in patients who underwent complete resection based on surgical impression and post-operative imaging. However, the recurrence rate went up to 90%, in the group of patients who underwent complete surgical resection based on surgeon's impression alone (i.e., without any radiological evidence of gross total excision). Partial resection of craniopharyngioma carries a 10-year recurrence risk of up to 85%.[3,16,17] It has been established in previous studies that tumor recurrence has a negative impact on overall survival.[18] Radiation therapy has been demonstrated to be an effective adjuvant modality to significantly reduce the risk of recurrence.[19] Until 1961, craniopharyngiomas were considered to be radio-resistant tumors. The efficacy of radiotherapy in craniopharyngiomas was first published by Kramer et al,[20] when he reported favorable outcome in a series of 10 patients who underwent a combination of minimal surgery and high-dose megavoltage (two million volt roentgen rays) irradiation.

10-year recurrence rates vary from 20 to 50% in tumors treated with surgery alone. It is well documented that recurrent tumors are associated with significantly higher risk and poorer outcome, with overall surgical mortality rates reported to be between 10.5 and 40.6%. Since craniopharyngiomas are radio-responsive, post-operative radiation therapy has consistently shown reduction in recurrence rates.[17,21–24] At the same time, conventional radiation therapy increases the rate of hypothalamic-pituitary disorders, and vascular abnormalities[25,26] leading to decreased somatic growth, obesity, and impaired mental and sexual development in children.[18,26–29] Some of the more recent studies have demonstrated that no significant difference in terms of pituitary morbidity when comparing surgery alone, or along with radiotherapy for craniopharyngiomas.[18,22,30]

However, it not clear whether radiation therapy should be employed immediately after surgery, or on recurrence of the tumor. A pediatric case series by Weiss et al indicates that radiation given immediately after surgery is preferable over radiation therapy on recurrence in terms of reduced morbidity and control.[31–34] In contrast, no significant difference in either tumor control or overall survival has been reported in adult patients with craniopharyngiomas who received radiation therapy adjuvantly or at progression. Thus, an early post-operative radiation therapy may be administered in children with tumors that are incompletely resected, whereas adult patients with craniopharyngiomas may receive radiation adjuvantly or at tumor recurrence. No clear guidelines currently exist about the optimal management of residual and recurrent craniopharyngiomas.

In our study, tumor control was seen in 91.4% (32 of 35 patients) after a mean radiological follow up of 62 months (median radiological follow up of 60.1 months). This confirms with data of previously published series by Mokry,[35] Chiou,[36] Kobayashi,[5] Niranjan,[37] Pikis[38] and other authors, which reported tumor control rates of 36–87.2% (**Table 4**).The 5-year progression free survival of 92.3% in radiation group of our study was also comparable to the rates observed in other studies. Pikis,[38] in a recent article showed maximum dose >35 Gy is associated with increased risk of post SRS neurological deficit. The 1 and 5-year progression free survival were found to be 100% and 92.3% respectively. No statistically significant difference was noted between progression free survival based on age of the patient, tumor type (solid vs. solid-cystic), tumor size, duration between surgery and gamma knife, or dose administered to the tumor. This might be attributed to the low sample size in our study. Kobayashi[5] and Lee[3] have demonstrated that large tumor volumes have a negative impact on probability of tumor control after gamma knife radiosurgery.

Optic apparatus is particularly sensitive to radiation, and tumors abutting the optic chiasm are a challenge to be treated with stereotactic radiosurgery. The dose to the tumor has to be reduced, and that might reduce the efficacy of GKRS. Strategies for such tumors can include surgical decompression to relieve the compression on the nerve followed by GKRS to the residual tumor. In case of tumors with cystic component, the solid component can be administered radiosurgery, while cyst decompressed with ommaya/catheter placement or intracavitary

Table 4
Previously published studies on radiosurgery for residual craniopharyngiomas.

Author	No. of patients	Mean Volume (mm3)	Median Follow up (months)	Tumor Control (%)	5-year Prog. Free Survival (%)	Morbidity (%)	Median Marginal Dose (Gy)
Mokry, 1999[35]	23	7000	23[a]	74	NA	0	10.8
Chung, 2000[11]	31	8900	33	87.2	NA	3.2	12.2
Chiou, 2001[36]	10	1700	63	58	NA	10	16.4
Amendola, 2002[6]	14	3700	39[a]	58	NA	0	14
Ulfarsson, 2003[7]	21	8000	161	36	NA	19	6
Niranjan, 2010[37]	46	1000	32	68.6	67.8	6	13
Kobayashi, 2012[5]	100	3500	63	79.6	61	6	11.5
Lee, 2014[3]	137	5500	45.7	69	70	8	12.0
Losa, 2018[4]	50	2100	65[a]	86	90.3	2	14.3
Pikis, 2021[38]	38	3350	43.5	58	50	6.2	13.26
Our Study	**35**	**3250**	**60.1**	**91.4**	**92.3**	**14**	**12**

[a] *Mean follow up.*

bleomycin. Some studies have shown the role of intracavitary irradiation using Phosphorus-32 and Yttrium-90 isotopes to collapse the cystic component of mixed solid-cystic tumors, while administering GKRS to the solid component for better tumor control.[39]

Treatment of craniopharyngioma is complex, and requires a multidisciplinary approach. In concordance with the existing literature, our observational study found good tumor control rates with GKRS for residual disease. Also, it showed better OS and PFS than the group that did not receive GKRS.

5. Limitations

The study had a relatively low sample size due to the lack of consensus regarding adjuvant radiation treatment in craniopharyngioma. This study is an observational study. Randomised controlled trials are needed to see definite benefits of GKRS for residual disease, and for timing of administration of GKRS. Also, the study does not compare the radiological, endocrine and ophthalmological outcome of patients with recurrent/residual disease who underwent radiosurgery, with those who underwent surgical excision of residual tumor. The follow-up period in the surgery alone group is relatively low; however we do have a longer follow up in GKRS group, and the 5-year PFS and OS in this group is better than the 3-year in patients that did not receive GKRS.

6. Conclusion

This study supports the existing evidence that gamma knife is a safe modality with excellent tumor control rates for residual craniopharyngiomas. It should be considered as standard of care for such tumors. Attempted gross total excision is associated with significant perioperative mortality. Given the significant number of patients (12–27%) requiring repeat surgical intervention at a later stage for recurrent disease, gamma knife radiosurgery seems to be a safe adjuvant treatment which can be offered to craniopharyngioma patients post-surgery.

CRediT authorship contribution statement

Saurabh Gupta: Conceptualization, Writing – original draft. **Deepak Agrawal:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Shweta Kedia:** Writing – review & editing. **Shashank Sharad Kale:** Supervision.

Declaration of competing interest

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

References

1. Merchant TE, Kun LE, Hua C-H, et al. Disease control after reduced volume conformal and intensity modulated radiation therapy for childhood craniopharyngioma. *Int J Radiat Oncol*. 2013;85(4):e187–e192. https://doi.org/10.1016/j.ijrobp.2012.10.030.
2. O'steen L, Indelicato DJ. Advances in the management of craniopharyngioma. *F1000Research*. 2018;7. https://doi.org/10.12688/f1000research.15834.1.
3. Lee C-C, Yang H-C, Chen C-J, et al. Gamma Knife surgery for craniopharyngioma: report on a 20-year experience. *J Neurosurg*. 2014;121(Suppl):167–178. https://doi.org/10.3171/2014.8.GKS141411.
4. Losa M, Pieri V, Bailo M, et al. Single fraction and multisession Gamma Knife radiosurgery for craniopharyngioma. *Pituitary*. 2018;21(5):499–506. https://doi.org/10.1007/s11102-018-0903-5.
5. Kobayashi T. Long-term results of gamma knife radiosurgery for 100 consecutive cases of craniopharyngioma and a treatment strategy. *Prog Neurol Surg*. 2009;22:63–76. https://doi.org/10.1159/000163383.
6. Amendola BE, Wolf A, Coy SR, Amendola MA. Role of radiosurgery in craniopharyngiomas: a preliminary report. *Med Pediatr Oncol*. 2003;41(2):123–127. https://doi.org/10.1002/mpo.10364.
7. Ulfarsson E, Lindquist C, Roberts M, et al. Gamma knife radiosurgery for craniopharyngiomas: long-term results in the first Swedish patients. *J Neurosurg*. 2002;97(5 Suppl):613–622. https://doi.org/10.3171/jns.2002.97.supplement5.0613.
8. Lee M, Kalani MYS, Cheshier S, Gibbs IC, Adler JR, Chang SD. Radiation therapy and CyberKnife radiosurgery in the management of craniopharyngiomas. *Neurosurg Focus*. 2008;24(5):E4. https://doi.org/10.3171/FOC/2008/24/5/E4.
9. Iwata H, Tatewaki K, Inoue M, et al. Single and hypofractionated stereotactic radiotherapy with CyberKnife for craniopharyngioma. *J Neuro Oncol*. 2012;106(3):571–577. https://doi.org/10.1007/s11060-011-0693-3.
10. Kobayashi T, Kida Y, Mori Y, Hasegawa T. Long-term results of gamma knife surgery for the treatment of craniopharyngioma in 98 consecutive cases. *J Neurosurg Pediatr*. 2005;103(6):482–488. https://doi.org/10.3171/ped.2005.103.6.0482.
11. Chung WY, Pan DH, Shiau CY, Guo WY, Wang LW. Gamma knife radiosurgery for craniopharyngiomas. *J Neurosurg*. 2000;93(Suppl 3):47–56. https://doi.org/10.3171/jns.2000.93.supplement3.0047.
12. Ellingson BM, Wen PY, Cloughesy TF. Modified criteria for radiographic response assessment in glioblastoma clinical trials. *Neurotherapeutics*. 2017;14(2):307. https://doi.org/10.1007/S13311-016-0507-6.
13. World Health Organization. *List of Official ICD-10 Updates Ratified October 2006*. 2006.
14. Mortini P, Losa M, Gagliardi F. Radical removal of craniopharyngiomas. Tumors cent nerv syst vol 9 lymphoma, supratentorial tumors, glioneuronal tumors, gangliogliomas, neuroblastoma adults, astrocytomas, ependymomas, hemangiomas, craniopharyngiomas. *January*. 2012:249–267. https://doi.org/10.1007/978-94-007-5488-1_29.
15. Tomita T, Bowman RM. Craniopharyngiomas in children: surgical experience at Children's Memorial Hospital. *Childs Nerv Syst*. 2005;21(8–9):729–746. https://doi.org/10.1007/S00381-005-1202-9.
16. Shi X-E, Wu B, Fan T, Zhou Z-Q, Zhang Y-L. Craniopharyngioma: surgical experience of 309 cases in China. *Clin Neurol Neurosurg*. 2008;110(2):151–159. https://doi.org/10.1016/j.clineuro.2007.10.013.
17. Fahlbusch R, Honegger J, Paulus W, Huk W, Buchfelder M. Surgical treatment of craniopharyngiomas: experience with 168 patients. *J Neurosurg*. 1999;90(2):237–250. https://doi.org/10.3171/jns.1999.90.2.0237.

18. Karavitaki N, Brufani C, Warner JT, et al. Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. *Clin Endocrinol*. 2005;62(4):397–409. https://doi.org/10.1111/j.1365-2265.2005.02231.x.
19. Minniti G, Esposito V, Amichetti M, Maurizi Enrici R. The role of fractionated radiotherapy and radiosurgery in the management of patients with craniopharyngioma. *Neurosurg Rev*. 2009;32(2):125–132. https://doi.org/10.1007/s10143-009-0186-4.
20. Kramer S, Mckissock W, Concannon JP. Craniopharyngiomas. Treatment by combined surgery and radiation therapy. *J Neurosurg*. 1961;18:217–226. https://doi.org/10.3171/JNS.1961.18.2.0217.
21. Mortini P, Losa M, Pozzobon G, et al. Neurosurgical treatment of craniopharyngioma in adults and children: early and long-term results in a large case series. *J Neurosurg*. 2011;114(5):1350–1359. https://doi.org/10.3171/2010.11.JNS10670.
22. Lin LL, Naqa I El, Leonard JR, et al. Long-term outcome in children treated for craniopharyngioma with and without radiotherapy. *J Neurosurg Pediatr*. 2008;1(2):126–130. https://doi.org/10.3171/PED/2008/1/2/126.
23. Lo AC, Howard AF, Nichol A, et al. Long-term outcomes and complications in patients with craniopharyngioma: the British columbia cancer agency experience. *Int J Radiat Oncol*. 2014;88(5):1011–1018. https://doi.org/10.1016/j.ijrobp.2014.01.019.
24. Conti A, Pontoriero A, Ghetti I, et al. Benefits of image-guided stereotactic hypofractionated radiation therapy as adjuvant treatment of craniopharyngiomas. *A review. Child's Nerv Syst.* 2018;August:1–9. https://doi.org/10.1007/s00381-018-3954-z.
25. Lo AC, Howard AF, Nichol A, et al. A cross-sectional cohort study of cerebrovascular disease and late effects after radiation therapy for craniopharyngioma. *Pediatr Blood Cancer*. 2016;63(5):786–793. https://doi.org/10.1002/pbc.25889.
26. Wijnen M, van den Heuvel-Eibrink MM, Janssen JAMJL, et al. Very long-term sequelae of craniopharyngioma. *Eur J Endocrinol*. 2017;176(6):755–767. https://doi.org/10.1530/EJE-17-0044.
27. Müller HL, Bueb K, Bartels U, et al. Obesity after childhood craniopharyngioma - German multicenter study on pre-operative risk factors and quality of life. *Klin Pädiatr*. 2001;213(4):244–249. https://doi.org/10.1055/s-2001-16855.
28. Bülow B, Attewell R, Hagmar L, Malmström P, Nordström C-H, Erfurth EM. Postoperative prognosis in craniopharyngioma with respect to cardiovascular mortality, survival, and tumor recurrence [1]. *J Clin Endocrinol Metab*. 1998;83(11):3897–3904. https://doi.org/10.1210/jcem.83.11.5240.
29. Sterkenburg AS, Hoffmann A, Gebhardt U, Warmuth-Metz M, Daubenbüchel AMM, Müller HL. Survival, hypothalamic obesity, and neuropsychological/psychosocial status after childhood-onset craniopharyngioma: newly reported long-term outcomes. *Neuro Oncol*. 2015;17(7):1029–1038. https://doi.org/10.1093/neuonc/nov044.
30. Merchant TE, Kiehna EN, Sanford RA, et al. Craniopharyngioma: the st. Jude children's research hospital experience 1984-2001. *Int J Radiat Oncol Biol Phys*. 2002;53(3):533–542. http://www.ncbi.nlm.nih.gov/pubmed/12062594. Accessed November 26, 2018.
31. Habrand JL, Ganry O, Couanet D, et al. The role of radiation therapy in the management of craniopharyngioma: a 25-year experience and review of the literature. *Int J Radiat Oncol Biol Phys*. 1999;44(2):255–263. http://www.ncbi.nlm.nih.gov/pubmed/10760417. Accessed November 26, 2018.
32. Moon SH, Kim IH, Park SW, et al. Early adjuvant radiotherapy toward long-term survival and better quality of life for craniopharyngiomas—a study in single institute. *Child's Nerv Syst.* 2005;21(8–9):799–807. https://doi.org/10.1007/s00381-005-1189-2.
33. Regine WF, Mohiuddin M, Kramer S. Long-term results of pediatric and adult craniopharyngiomas treated with combined surgery and radiation. *Radiother Oncol*. 1993;27(1):13–21. http://www.ncbi.nlm.nih.gov/pubmed/8327728. Accessed November 26, 2018.
34. Weiss M, Sutton L, Marcial V, et al. The role of radiation therapy in the management of childhood craniopharyngioma. *Int J Radiat Oncol Biol Phys*. 1989;17(6):1313–1321. https://doi.org/10.1016/0360-3016(89)90543-9.
35. Mokry M. Craniopharyngiomas: a six year experience with Gamma Knife radiosurgery. *Stereotact Funct Neurosurg*. 1999;72(Suppl 1):140–149. https://doi.org/10.1159/000056450.
36. Chiou S-M, Lunsford LD, Niranjan A, Kondziolka D, Flickinger JC. Stereotactic radiosurgery of residual or recurrent craniopharyngioma, after surgery, with or without radiation therapy. *Neuro Oncol*. 2001;3(3):159–166. https://doi.org/10.1093/neuonc/3.3.159.
37. Niranjan A, Kano H, Mathieu D, Kondziolka D, Flickinger JC, Lunsford LD. Radiosurgery for craniopharyngioma. *Int J Radiat Oncol Biol Phys*. 2010;78(1):64–71. https://doi.org/10.1016/j.ijrobp.2009.07.1693.
38. Pikis S, Mantziaris G, Lavezzo K, Dabhi N, Sheehan J. Stereotactic radiosurgery for craniopharyngiomas. *Acta Neurochir*. 2021;163(11):3201–3207. https://doi.org/10.1007/s00701-021-04990-1.
39. Yu X, Liu Z, Li S. Combined treatment with stereotactic intracavitary irradiation and gamma knife surgery for craniopharyngiomas. *Stereotact Funct Neurosurg*. 2000;75(2–3):117–122. https://doi.org/10.1159/000048392.

Abbreviations

GKRS: Gamma Knife Radiosurgery
PFS: Progression Free Survival
OS: Overall Survival
RANO: Response Assessment in Neuro-Oncology
CEMRI: Contrast-enhanced Magnetic Resonance Imaging