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Original Article

Effects of two different radiotherapies for craniopharyngiomas using stereotactic radiosurgery/stereotactic radiotherapy or fractionated stereotactic radiotherapy

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ABSTRACT

Background: Numerous studies have reported about good tumor control with both stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (FSRT) for residual and recurrent craniopharyngiomas, but no studies have reported on the appropriate use of different types of radiation modalities. This study aimed to report the outcomes of SRS/stereotactic radiotherapy (SRT) or FSRT and compare tumor control in a single center.

Methods: From 2014 when TrueBeamTM STx with Novalis was introduced in our hospital to 2021, 21 patients underwent SRS/SRT or FSRT with gamma knife surgery (GKS) and Novalis. We have selected the radiation modalities considering mainly the distance of the optic nerve and chiasm. Imaging and clinical follow-up data were sent and reviewed.

Results: The mean age was 52 years and there were 11 men. Of the 21 total patients, three experienced SRS (GKS, 50% isodose 12–15 Gy), five underwent SRT (GKS or Novalis, 19.5–24 Gy 3 fractions), and 13 patients underwent FSRT (Novalis, 54 Gy 30 fractions). The median follow-up was 32.6 (range 17–44) months after SRS/SRT and 34.0 (range 4–61) months after FSRT. In the SRS/SRT group, the mean tumor volume decreased from 1.103 to 0.131 cm^3 ($P < 0.01$), and in the FSRT group, from 3.015 to 1.012 cm^3 ($P < 0.01$). No radiation-induced optic neuropathy and other acute toxicity occurred.

Conclusion: Craniopharyngioma can be expected to have very good tumor control by selecting SRS/SRT or FSRT depending on the distance between the optic nerve and the tumor.

Keywords: Craniopharyngioma, Fractionated stereotactic radiotherapy, Gamma knife surgery, Long-term tumor control, Optic nerve

INTRODUCTION

Craniopharyngiomas are epithelial tumors that arise from squamous epithelial remnants of the Rathke pouch. Despite their histologically benign and growing slowly, they often cause clinical disorders such as visual and hypothalamic impairment and hypopituitarism. Its gold standard of treatment is surgical resection;[11,13,27] however, complete removal can result in severe damage

to visual and endocrine functions. To maintain long-term tumor control after surgical resection, adjuvant radiation therapy (RT) is commonly adopted.

Both stereotactic radiosurgery (SRS).[4,16,20] and fractionated stereotactic radiotherapy (FSRT).[2,6,23] for residual or recurrent craniopharyngiomas have been proven to be effective in the long-term overall and recurrence-free survival. Gamma knife surgery (GKS) delivers highly focused radiation and enables tumor control for cases that were difficult to remove or cases of recurrence. Moreover, recent development of stereotactic irradiation technology such as linear accelerator (linac) represented by TrueBeamTM STx with Novalis (Novalis) has provided maximum tumor control but minimum radiation injury. Although radiotherapy has becoming established, few definitive studies have focused on the selection criteria and comparison of the treatment results within the same institution.

From 2014 when Novalis was introduced in our hospital, we have selected SRS/stereotactic radiotherapy (SRT) with GKS or FSRT with Novalis considering mainly the distance of the optic nerve and chiasm. To the best of our knowledge, this is the first comparative single-center study of the treatment of craniopharyngiomas using GKS and linac-based stereotactic irradiation. We present the effect of this different RT and present an appropriate patient-specific treatment plan.

MATERIALS AND METHODS

From April 2014 to December 2021, 21 patients with histologically confirmed craniopharyngioma were treated for residual or recurrent craniopharyngioma using GKS or linac at Yokohama Rosai Hospital. In selecting the optimal dose and number of fractions, we have placed the highest priority on the distance between the optic nerve/optic chiasm and the tumor. The maximum dose applied to the optic nerve and chiasm was ≤8 gray (Gy). Patient's treatment was selected according to the following policies:

1. SRS/SRT was selected when the distance was far from several millimeters
2. FSRT was selected when the tumor is touching or compressing the optic tracts
3. Other selection criteria are as follows: Multisession GKS was performed when the residual or recurrence craniopharyngioma, especially the cyst component, had been growing rapidly.

Both SRS and SRT are strategies based on the concept of increasing the single dose or dose per fraction and shortening the total treatment period. FSRT, on the other hand, is a strategy based on the concept of reducing the dose per fraction, giving priority to tissue tolerance, and achieving tumor control by performing multiple irradiations. For this reason, we combined SRS and SRT into one strategy.

GKS technique

GKS was performed using a Leksell Gamma Knife Perfexion (Elekta Instrument AB, Stockholm, Sweden) and multisession GKS was performed with the Gamma Knife Extend System.[22] The Leksell GammaPlan TM System planning system was used, based on 1.0-mm-thick magnetic resonance imaging (MRI) slices and computed tomography. In cases of single-fraction GKS, a prescription dose of 12–15 Gy (median 13) was applied at the 50% isodose line; in cases of multisession GKS, a prescription dose of 6.5 Gy of three fractions was applied at the 50% isodose line for 3 consecutive days.

FSRT technique

The gross tumor volume was defined as the contrast-enhanced lesion on T1-weighted MRI. The clinical target volume (CTV) was expanded to a larger planning target volume (PTV), which included the CTV with a safety margin of 1–2 mm (median 1). HybridArc plans[14] were generated using the Brainlab iPlanDose treatment planning system, and 54 Gy was applied in conventional fractionation with a single dose of 1.8 Gy 5 times per week, and the whole treatment process took 6 weeks. In this study, in one pediatric patient who underwent RT with Novalis for three fractions, the treatment was classified SRT.

Imaging and clinical follow-up information were sent and reviewed at our center. Standard informed consent relating to summarizing radiation effects on craniopharyngiomas was obtained for each patient. We focused on imaging data, visual acuity, visual field, and endocrine function before and after RT. Computed tomography (CT) is performed if MRI is not available. Follow-up examinations were scheduled every 3 months to 1 year and obtained directly or from referring physicians. The tumor volume was calculated from pre- and post-treatment MRI or CT scans by contouring the lesion on each slice of a contrast-enhanced, T1-weighted MRI axial scan using the "volume" function in the "measurements" window of the GammaPlan software. Each tumor was classified into five groups after radiation:[4-6,21,23] complete response (CR and tumor disappeared), near complete response (NCR, >80% decrease in overall tumor volume), partial response (PR, <80% or >40% decrease in the overall volume), stable (stable, <40% decrease or <5% increase in the overall volume), or tumor progression (TP, >5% increase in the overall volume). We assessed the tumor control rates (CR, NCR, PR, and stable vs. TP) and overall response rates (CR and NCR vs. PR, stable, and TP). In this study, recurrence was defined as the appearance and growth of tumors out of the field. Endocrinopathies were defined as deficiencies requiring supplementary medication and confirmed by laboratory screening.

Statistical analysis

Statistical analyses were performed using R programming.[10] Fisher's exact test and Mann–Whitney U test were used to analyze differences in SRS/SRT and FSRT [Table 1]. Logistic regression was also performed to examine the differences in tumor control rates (CR, NCR, PR, and stable vs. TP) and in overall response rates (CR and NCR vs. PR, stable, and TP) according the following variables [Table 2]: patient age (<50 vs. ≥50 years), radiation types (SRS/SRT vs. FSRT), timing (adjunctive vs. salvage treatment), nature of the tumor (solid vs. others), presence or absence of calcification, tumor volume, distance between the tumor and the optic nerve (<1.5 vs. ≥1.5 mm). Probability values <0.05 were considered significant. Kaplan–Meier plots for tumor control were constructed based on the time of RT and date of tumor enlargement or last image evaluation if the tumor was controlled [Figure 1]. Non-tumor control was defined as the TP group. Wilcoxon's signed-rank test was used to compare tumor volume before and after RT.

RESULTS

Patient characteristics are summarized in Table 1. This retrospective study included 18 patients who underwent surgery at another hospital, and three patients at our hospital. There were two pediatric (aged <18 years) and 19 adult patients. The mean age was 52 (median 63, range 9–85) years and there were 11 men (52.4%). All patients had undergone at least one surgical intervention; 17 patients underwent open surgery, three underwent endoscopic endonasal surgery (EES), and one received both open surgery and EES. Of the 21 (19.0%) patients, four achieved gross total resection (GTR) and nine who received subtotal resection (STR), followed by adjuvant treatment immediately after surgery as part of their initial therapy. Twelve patients received salvage RT for recurrent or growing residual tumors. The mean period between primary surgery resection and salvage RT was 33 (4–95) months. Surgery and GKS were performed in one patient who needed an additional GKS out of the previous field. Solid and cystic components of tumor were identified on MRI, 7 (33.3%) patients had solid tumor, 9 (42.9%) had cystic tumor, and 5 (23.8%) had both solid and cystic tumors. Fourteen (66.7%) tumors were suprasellar and 7 (33.3%) were both intrasellar and suprasellar. No tumors localized to intrasellar.

Three patients experienced SRS (GKS, 50% isodose 12–15 Gy), five underwent SRT (GKS or linac, 19.5–24 Gy for three fractions), and 13 underwent FSRT (linac, 54Gy 30 fractions). One pediatric patient received SRS under general anesthesia. The median follow-up was 32.6 (range 17–44)

Table 1: Patient and tumor characteristics of each group who received SRS/SRT and FSRT.

	SRS/SRT	FSRT	Total	*P*-value
No. of cases (%)	8 (38.1)	13 (61.9)	21	
Age, median (range) (year)	48 (9–74)	63 (26–85)	63 (9–85)	0.856
Sex, Male/Female no (%)	3/5 (37.5/62.5)	8/5 (61.5/38.5)	11/10 (52.4/47.6)	0.387
Follow-up period, median (range) (month)	32.6 (17–44)	34.0 (4–61)	34 (4–61)	0.856
Prior treatment, no (%)				
One surgical resection	7 (87.5)	11 (84.6)	18 (85.7)	
Surgical resection 2 times	0 (0)	1 (7.7)	1 (4.8)	
Surgical resection and Ommaya reservoir	0 (0)	1 (7.7)	1 (4.8)	
GKS	1 (12.5)	0 (0)	1 (4.8)	
Extent of last resection, no (%)				
Complete	3 (37.5)	1 (7.7)	4 (19.0)	0.253
Subtotal	5 (62.5)	12 (92.3)	17 (81.0)	
Timing of radiation treatment, no (%)				
Adjuvant treatment	2 (25.0)	7 (53.8)	9 (42.9)	0.367
Salvage treatment	6 (75.0)	6 (46.2)	12 (57.1)	
Tumour volume (cm^3)				0.0535
Mean	1.103	3.051	2.309	
Median	0.652	2.428	1.750	
Range	0.094–3.541	0.048–11.675	0.048–11.675	
Distance of optic nerve (mean)/(median) (mm)	2.19/1.80 (0–7)	0.15/0 (0–1)	0.93/0 (0–7)	0.00037
Symptoms before radiotherapy				
Visual acuity deterioration, no (%)	2 (25.0)	7 (53.8)	9 (42.9)	0.367
Visual field deterioration, no (%)	6 (75.0)	7 (53.8)	13 (61.9)	0.400
Endocrine deterioration, no (%)	6 (75.0)	8 (61.5)	14 (66.7)	0.656

SRS: Stereotactic radiosurgery, SRT: Stereotactic radiotherapy, FSRT: Fractionated stereotactic radiotherapy, GKS: Gamma knife surgery

Table 2: Factors associated with overall response rates (CR and NCR vs. PR, stable and PD) (*n*=21).

Variables	Univariate *P* value	Multivariate *P* value	Odds ratio	95% CI
Patient age (<50 vs. ≥50)	1.000	0.998	-	-
Radiation types (SRS/SRT vs. FSRT)	0.018	0.998	-	-
Timing (adjuvant vs. salvage)	0.397	0.960	0.891	0.01-82.90
Nature of the tumor (solid vs. others)	0.361	0.998	-	-
Presence of calcification (vs. non)	0.174	0.998	-	-
Tumor volume (continuous)	1.000	0.939	0.977	0.53-1.79
Distance between tumor and optic nerve (<1.5 vs. ≥1.5 mm)	0.123	1.370	-	-

CR: Complete response, NCR: Near complete response, PR: Partial response, TP: Tumor progression, SRS: Stereotactic radiosurgery, SRT: Stereotactic radiotherapy; FSRT, Fractionated stereotactic radiotherapy

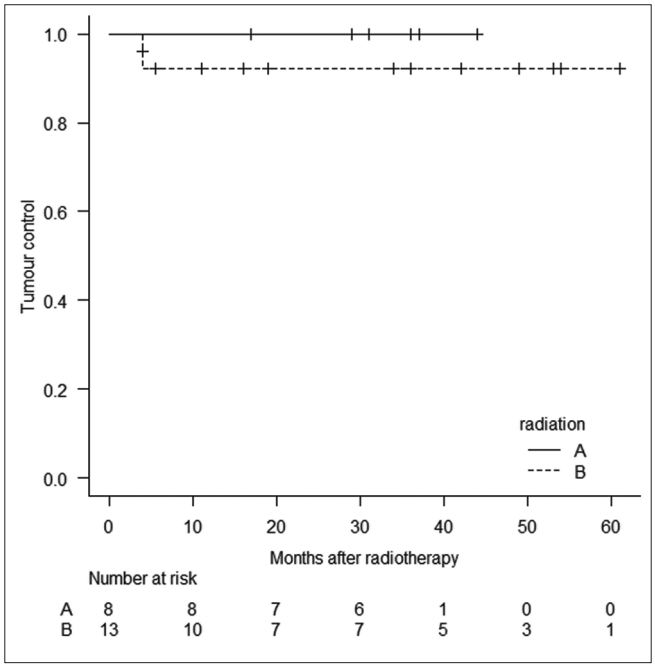

Figure 1: Kaplan–Meier analysis demonstrating local tumour control after stereotactic radiosurgery/stereotactic radiotherapy (SRS/SRT) (a) and Fractionated stereotactic radiotherapy (b). Both of them are effective and good tumor control has been achieved.

months after SRS/SRT and 34.0 (range 4–61) months after FSRT. Table 1 compares the baseline characteristics between the two treatments. The distance between the tumor and the optic nerve showed significant differences depending on the radiation type ($P < 0.001$). In the SRS/STR group, the mean and median tumor volume were 1.103 and 0.652 (range 0.094–3.541) cm^3, respectively, and in the SFRT group, the values were 3.051 and 2.428 (range 0.048–11.675) cm^3, respectively. At the final assessment, all patients but four were alive, but the causes of their deaths were not related to this disease.

In the SRS/SRT group, the final radiation outcomes were CR in 37.5% and NCR in 62.5%. In the FSRT group, the outcomes were CR in 7.7%, NCR in 38.5 %, PR in 38.5%, stable in 7.7%, and TP in 7.7% of the cases [Table 3]. In the SRS/SRT group, the mean and median tumor volume decreased from 1.103 to 0.131 cm^3 and from 0.652 to 0.032 cm^3 ($P < 0.01$), respectively, and the FSRT group, the values decreased from 3.015 to 1.012 cm^3 and from 2.428 to 0.289 cm^3 ($P < 0.01$). Figures 2 and 3 depict illustrative cases. According to the definition of recurrence, the cystic tumor in one patient who had Ommaya reservoir grew regardless of puncturing it during irradiation; however, almost all patients achieved good tumor control.

Both types of RT result in great tumor control [Table 3]. The tumor control rate (CR, NCR, PR, and stable vs. TP) was 95.2%. In the univariate analysis, none of the following factors were associated with overall response rate (CR and NCR vs. PR, stable, and TP) [Table 2], patient age (<50 vs. ≥50), timing (adjunctive vs. salvage treatment), nature of the tumor (solid vs. others), presence or absence of calcification, tumor volume, and distance between the tumor and the optic nerve (<1.5 vs. ≥1.5 mm) (all $P \geq 0.05$). In this study, the overall response rate tended to be better in the SRS/SRT group, whereas no significant difference was found concerning tumor control in the multivariate analysis [Table 2]. Kaplan–Meier curves showed that both SRS/SRT and FSRT were effective [Figure 1].

No radiation-induced optic neuropathy, acute toxicity, and other adverse events such as radiation necrosis and cyst formation occurred after SRS/SRT and FSRT. During follow-up, visual acuity was improved in 1 (4.8%) patient who underwent FSRT, and visual field defects were improved in 3 (14.3%) patients. Pituitary function remained unchanged during follow-up. Because formal neurocognitive testing was not obtained from all patients, data concerning cognitive toxicity could not be retrospectively extracted. During follow-up, further treatment included GKS was not needed. Only one patient with enlarged tumor died from another factor and follow-up period was 4 months.

DISCUSSION

Craniopharyngiomas are histologically benign and are slowly progressive, but GTR is challenging because of the anatomical

Table 3: The difference of tumor control between SRS/SRT and FSRT.

	CR tumor disappeared (%)	NCR>80% decrease (%)	PR<80% or>40% decrease (%)	Stable<40% decrease or<5% increase (%)	TP>5% increase (%)
SRS/SRT	3 (37.5)	5 (62.5)	0 (0)	0 (0)	0 (0)
FSRT	1 (7.7)	5 (38.5)	5 (38.5)	1 (7.7)	1 (7.7)

SRS: Stereotactic radiosurgery, SRT: Stereotactic radiotherapy, FSRT, fractionated stereotactic radiotherapy, CR: Complete response, NCR: Near complete response, PR: Partial response, TP: Tumor progression

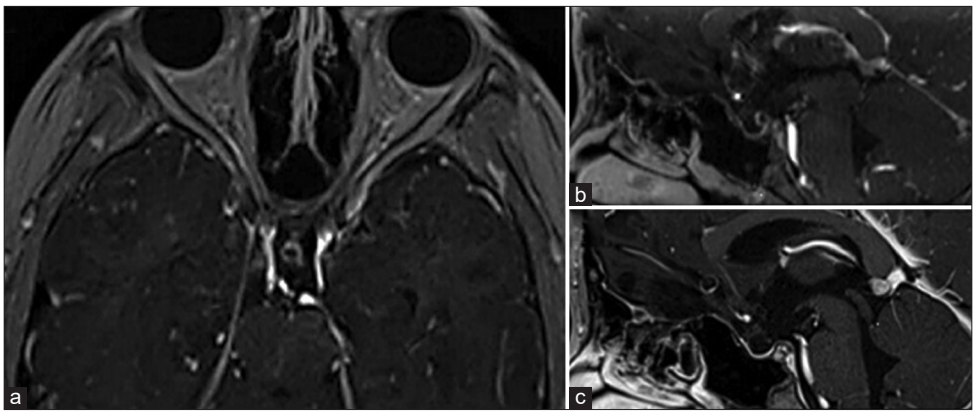

Figure 2: A 10-years-old girl underwent craniotomy 33 months ago. The recurrent tumor was on the dorsal side of the optic chiasm and the distance between the tumour and chiasma was 2 mm (a and b). We selected stereotactic radiosurgery under general anesthesia. No visual impairment occurred within the 17-month follow-up period, the tumor disappeared (c).

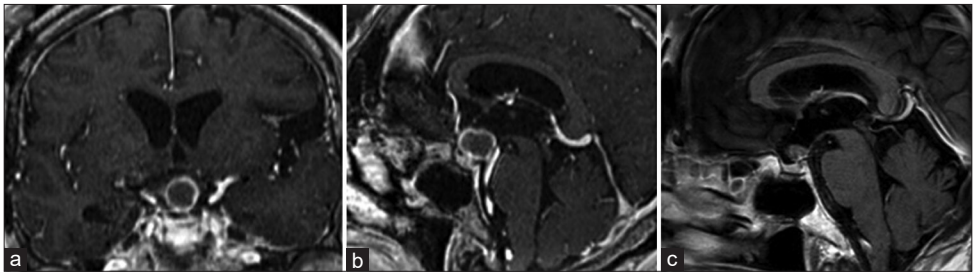

Figure 3: A 65-year-old woman received radiation therapy 32 months after surgery. The residual tumor was cystic but did not grow fast. The tumor compressed the optic nerve and it was relatively large (a and b), so we selected 30 fractions, and tumor control was great 54 months after fractionated stereotactic radiotherapy (c).

position, that is, the tumor is located very close to the optic apparatus, pituitary, and critical vascular structures. RT such as GKS and linac has been proven to be effective as salvage methods for residual and recurrent craniopharyngiomas. This tumor has been considered good candidates for RT; however, there are several clinical challenges to achieve a long-term tumor control.

First, the sufficient dose to achieve good long-term tumor control without causing visual dysfunction is not yet clarified. GKS has been reported to be an effective management option and studies have suggested 5-year progression-free survival rate of 72.1–90.3%.[4,16,20,26] However, these studies focused on one treatment and the comparison of outcomes from other radiation strategies and criteria for selecting treatment plans have not been established. GKS was mainly performed in a single fraction and it can threaten visual function when the tumor was touching or compressing the optic nerve.[7] The tolerance dose of the optic nerve in SRS has been previously reported to be 8 Gy.[25] However, since then, technological improvements in imaging, radiation planning, and treatment delivery have made it possible to safety apply >8 Gy to optic nerve. Hasegawa *et al.* reported that the overall radiation-induced optic neuropathy was 5% and most of them were in the high-dose group (≥15 Gy). Only one patient who

received 8≤ Gy developed adverse effects of visual function and had undergone previous 60 Gy-fractioned RT. They insisted that visual safety was secured by limiting the dose to <14 Gy; however, the tolerance dose of the optic apparatus is usually lower than the dose required to successfully treat the majority of tumors. In that study, almost half of the patients had a tumor recurrence, resulting in treatment failure during the long-term period due to the reduced marginal dose of ≤10 Gy when the tumors adhered to the optic apparatus. Similar outcomes were reported in other studies in which higher margin dose (≥12 Gy) enables better local tumor control,[20] but sufficient distance to the optic nerve (≥2 mm, ≥3 mm or 3–5 mm)[6,7,19,20] is necessary to achieve that.

On the contrary, using FSRT rather than SRS, it becomes possible to treat tumors safety when they are in contact with the optic nerve or when it is difficult to identify the optic pathway on the image. FSRT also minimizes toxicity to normal tissues and enables treatment of large tumors. A reduction of marginal dose can be possible compared with before, which brought a smaller PTV and higher doses to the target with normal tissues were spared.[17] In treatments with multiple fractions, studies have indicated that the risk of visual complications increases with the dose of >60 Gy.[19] We have selected multi-fraction therapy with 54 Gy when the tumor was just touching or compressing the optic nerve, but sometimes, we chose SRT considering the speed of the tumor growth, especially cystic tumors. Multisession GKS appears as effective as single-fraction GKS,[16] making it possible to treat with an effective dose without over irradiation. When RT should be completed immediately considering the speed of tumor progression or patient's general condition, 19.5 Gy with three fractions has been selected in our institution. Studies have reported similar or slightly lower rate of visual damage using fractionated GKS.[4,7] Milano *et al*. reported that radiation-induced optic nerve injury risks are low (<1%) with optic apparatus maximum point dose <10 Gy in one fraction, 20 Gy in three fractions, and 25 Gy in five fractions in patients without prior RT.[18]

As mentioned above, FSRT is much effective in the case that it is difficult to identify the optic pathway. However, tumors with cystic growth may be challenging to control because FSRT must take a long time. The previous studies have indicated tumor enlargement during or after the treatment, especially in craniopharyngiomas with cystic components.[1,8,12] A group of pediatric patients with this tumor received proton beam therapy and intensity-modulated RT after RT. In 52 patients, 40% had cyst growth during RT and 20% required intervention such as cyst decompression or adaptive replanning.[3] Another report showed close observation for cyst growth of pediatric craniopharyngiomas. Of the 21 patients, 52.4% had tumor enlargement (mostly cystic component). The median time to maximal tumor expansion was 1.5 (range, 1.0–5.0) months and the median volume increase was 33.9% (range 15.6–224.4%).[24]

Patterns of cystic changes are classified into two types: early yet transient growth and slowly progressive and late growth. Early cyst growth seems to be appeared within 3 months during or after RT, and frequent surveillance imaging during RT is needed. This type is temporary and spontaneous decompression is obtained over time, whereas late cyst growth was related to visual and hypothalamic toxicities (P = 0.009 and 0.04) on the multivariate analysis.[3] No studies have reported significant difference in cyst growth in relation to the types of RT. These studies have shown the possibility that the cystic tumor does not respond to RT in the same way as the solid component.[24] Bishop *et al*. described that it is crucial to recognize transient cyst growth to prevent unnecessary surgical intervention.[3] Based on these reports that cystic tumors grow during irradiation, we propose to consider the following three points: first, adding a sufficient safety margin in anticipation of the cyst growth is possible because of the low-dose RT in FSRT. Second, re-examination of images and replanning is conducted if necessary. Finally, SRS/SRT is selected in cases in which the distance between the optic nerve and the tumor is away from 2 to 3 mm.

A smaller cyst volume should be associated with better tumor control.[9] An analysis of adult patients with cystic craniopharyngiomas concluded that the use of the Ommaya reservoir with SRT could minimize radiation exposure to the optic apparatus and brain stem.[8,12,15]

In this study, only one tumor was identified to have enlarged and categorized as TP, which was mainly a cystic lesion. We selected FSRT because the tumor compressed the optic nerve. In the case that the cystic component enlarged, the CTV margin was determined as 2 mm. Moreover, the patient had Ommaya reservoir and the cystic component was punctured during the treatment to reduce the volume. Four months later, MRI showed tumor progression compared with before RT. Although the observation period was short, it was the latest evaluation, and we judged it to be uncontrolled.

In this study, we have selected types of radiation based on the distance between the tumor and the optic nerve. Improved RT techniques over time have brought remarkable results in tumor control and enable treatment more safety. We can achieve long-term tumor control while maintaining the quality of life in many cases by changing the treatment and intervention according to each case. To the best of our knowledge, this is the first report to describe treatment options for gamma knife and linac in a single center.

Limitation

This study has several limitations mainly due to its small number of patients, especially pediatrics. We have not yet

encountered cases requiring general anesthesia for FSRT in children. No patients developed a new pituitary deficiency because few pediatric cases were reported in this report. Moreover, visual disturbance generally occurs within 3 years after radiation,[17,20] and our follow-up period may be too short to evaluate it.

CONCLUSION

Craniopharyngiomas are radiosensitive. The distance between the tumor and the optic nerve is the most important factor in treatment selection. The cystic component, speed of the tumor growth, and general condition of the patient may affect treatment choices. Appropriate management and selection of irradiation methods tailored to each patient appeared to provide a better long-term tumor control.

Acknowledgments

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Consent to participate

For this type of study, written consent was not required. Standard informed consent was obtained and this study was reviewed and approved by the Institutional Review Board of Yokohama Rosai Hospital (# 2022-18).

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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