Acta Neurochirurgica (2024) 166:218
https://doi.org/10.1007/s00701-024-06113-y

ORIGINAL ARTICLE

Long-term outcomes of neuroendoscopic cyst partial resection combined with stereotactic radiotherapy for craniopharyngioma

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Received: 13 February 2024 / Accepted: 5 May 2024

Abstract

Purpose The aim of this study was to evaluate the treatment outcomes of neuroendoscopic cyst partial resection (ECPR) combined with stereotactic radiotherapy (SRT) for cystic craniopharyngiomas.

Methods In this retrospective study, 22 craniopharyngioma patients undergoing ECPR combined with SRT were included. This combination therapy was indicated for suprasellar cystic craniopharyngiomas in patients whose pituitary function was preserved but would be difficult to preserve in direct surgery. The outcomes of combination therapy, including tumor control and postoperative visual and pituitary functions, were investigated.

Results ECPR was safely performed, and cyst shrinkage was accomplished in all cases. After ECPR, visual function improved in 12 of 13 patients (92%) with visual field disturbance and did not deteriorate in any patients. Pituitary function was preserved in 14 patients (64%) and deteriorated in eight patients (36%) after ECPR. As a complication of ECPR, meningitis occurred because of a wound infection in one patient. In 18 of 22 patients (82%), the tumor was controlled without further treatment 19 – 87 months (median, 33 months) after SRT. Hypopituitarism was an adverse event after SRT in two of the 18 patients who achieved tumor control. Four patients (18%) had enlarged cysts after SRT. Postoperative pituitary function was significantly more likely to deteriorate in cases of extensive detachment from the ventricular wall, and retreatment was significantly more common in cases with hypothalamic extension.

Conclusion Although limited to some cases, ECPR combined with SRT is a less invasive and useful therapeutic option for suprasellar cystic craniopharyngiomas. However, its long-term prognosis requires further evaluation.

Keywords Craniopharyngioma · Neuroendoscopy · Stereotactic radiotherapy · Treatment outcome · Complication

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Published online: 15 May 2024

Introduction

The first choice of treatment for craniopharyngioma is radical resection. In the past, craniotomy was the predominant surgical approach utilized to treat craniopharyngiomas, but a worldwide shift toward an extended transsphenoidal approach is in progress. It has been reported that extended transsphenoidal surgery improves the rate of tumor removal and reduces the complication rate because it does not require brain traction to remove the tumor and allows direct observation of the tumor below the optic nerve [6, 34, 42].

However, when a craniopharyngioma is completely removed, it is often difficult to preserve the pituitary stalk, and even if it is anatomically preserved, its function is often impaired [9, 42]. We previously reported that the pituitary stalk was preserved in only 30.8% of patients after radical resection by extended transsphenoidal surgery for suprasellar craniopharyngiomas, and pituitary function was preserved in only approximately half of these patients [39, 40]. Hypopituitarism and diabetes insipidus were found to be related to high mortality in craniopharyngioma patients by a nationwide population-based study in Sweden [26]. Moreover, in cases of craniopharyngioma with hypothalamic involvement, total tumor removal poses the risk of not only hypopituitarism but also hypothalamic injury. Hypothalamic injury causes hormonal disorder, memory disturbance, hypothalamic obesity, daytime sleepiness, behavioral change, and imbalances in the regulation of thirst, body temperature, heart rate, and blood pressure. These factors are related to morbidity and impairment of quality of life. Therefore, "hypothalamus-sparing surgery", including pituitary function, has been recommended in craniopharyngioma patients with hypothalamic involvement on MRI [6, 7, 20, 31]. In addition, extended transsphenoidal surgery carries a high risk of spinal fluid leakage and is particularly invasive in the elderly [10, 13, 38].

Although craniopharyngiomas are known to have a high recurrence rate following partial resection, a high rate of small tumor control by stereotactic radiotherapy (SRT) has been reported [5, 41, 43]. For this reason, it has recently been proposed that craniopharyngiomas involving the hypothalamus should be controlled by a combination treatment of partial surgical resection and SRT to avoid hypothalamic injury and dysfunction [31, 33].

Neuroendoscopic surgery for cystic craniopharyngioma was reported by Hellwig et al. in 1995, and there have been several reports since then. Although this method is less invasive than extended transsphenoidal surgery, there have been only a few reports on long-term outcomes in large numbers of patients treated with this method in combination with radiotherapy [2, 4, 8, 14, 19, 21–24, 29, 30, 36, 37]. Although neuroendoscopic cyst partial resection (ECPR) is indicated only for suprasellar cystic craniopharyngiomas, it can be an alternative treatment option if tumor control can be achieved with a combination of ECPR and SRT.

In the present study, we reviewed a series of suprasellar cystic craniopharyngioma patients who underwent ECPR and postoperative SRT.

Patients and methods

Study design and patients

Patients with cystic craniopharyngioma who underwent ECPR followed by SRT between 2007 and 2019 were included in this study. Patients who underwent ECPR but did not subsequently undergo radiotherapy were excluded. However, in patients whose craniopharyngioma recurred after undergoing ECPR alone and who underwent a second ECPR procedure followed by SRT, the second ECPR procedure was evaluated. SRT was performed using the CyberKnife system (Accuray, Sunnyvale, CA, USA) after ECPR. MRI follow-up was performed every 6 months after SRT and every year after one year post-SRT if there was no tumor regrowth. Finally, patients treated with ECPR and postoperative SRT were examined for changes in visual function after surgery, changes in pituitary function and long-term tumor control after SRT. Additionally, factors associated with postoperative hypopituitarism and retreatment were investigated (Fig. 1).

Indications for combined ECPR and SRT

The indications for ECPR were determined comprehensively based on the following conditions: 1) visual impairment or obstructive hydrocephalus due to craniopharyngioma, or progression of craniopharyngioma; 2) tumors mainly composed of a cystic component close to the third ventricle and accessible by the neuroendoscopic transventricular approach; 3) completely or partially preserved preoperative pituitary function, anticipated difficulty in preserving the pituitary stalk intraoperatively in direct surgery, especially in cases of retroinfundibular or transinfundibular craniopharyngioma [16], and 4) for elderly patients who prefer to avoid invasive extended transsphenoidal surgery. Therefore, ECPR was initially indicated for elderly patients who prefer to avoid relatively invasive extended transsphenoidal surgery, especially those with normal pituitary function. Subsequently, since we had become accustomed to using ECPR for craniopharyngiomas, we began to adapt it for younger

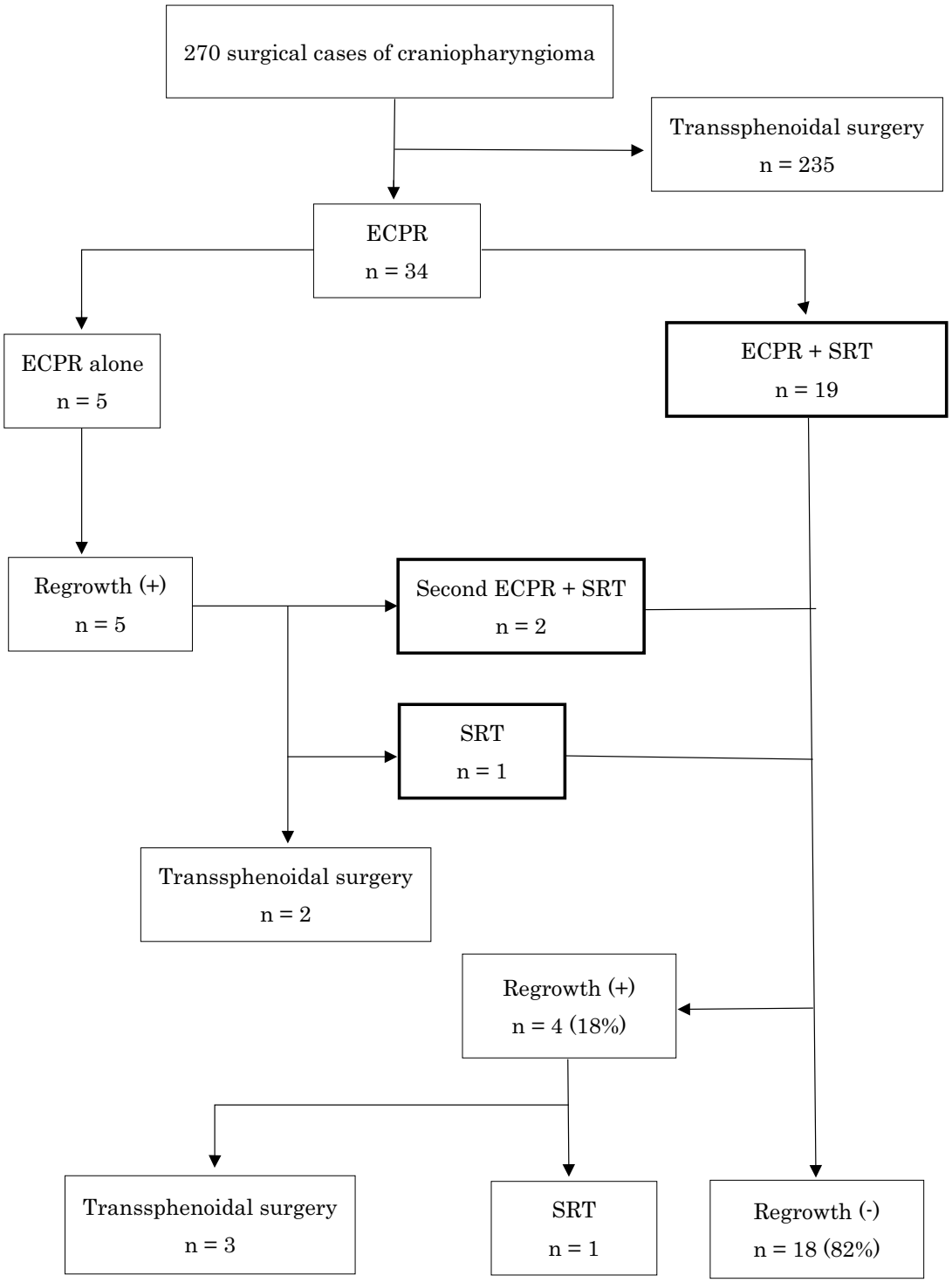

Fig. 1 Flowchart illustrating the outcomes of craniopharyngioma patients treated with a combination of neuroendoscopy and stereotactic radiotherapy. ECPR: neuroendoscopic cyst partial resection. SRT: stereotactic radiotherapy. A total of 22 patients with craniopharyngioma who underwent SRT after ECPR were evaluated. In these 22 patients, SRT was performed after the second ECPR in two patients and after regrowth in one patient. The bold-outlined section in the figure represents the 22 cases included in the analysis

patients whose pituitary function was maintained or elderly patients whose pituitary gland function was impaired. However, we generally performed extended transsphenoidal surgery, especially in young people with partially impaired pituitary function, because the procedure is more radical [40]. As discussed below, since SRT was not performed

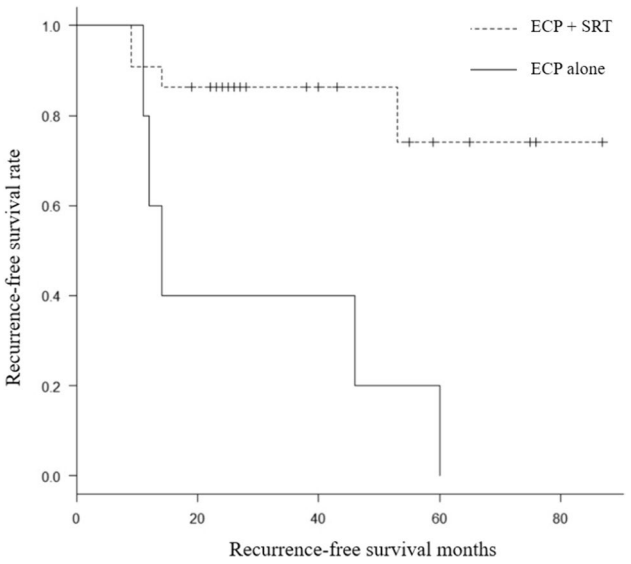

Fig. 2 Kaplan–Meier curve after neuroendoscopic cyst partial resection with or without stereotactic radiotherapy. ECPR: neuroendoscopic cyst partial resection. SRT: stereotactic radiotherapy. Craniopharyngiomas recurred in five patients who underwent ECPR alone without SRT

at the beginning of ECPR for craniopharyngiomas and the tumors often recurred, SRT was employed in combination (Fig. 2).

Surgical techniques for ECPR

The surgery was performed using a flexible fiberscope (Neu-4L; Machida Endoscope Co., Ltd., Tokyo, Japan) and videoscope (VEF type V; Olympus, Tokyo, Japan). The neuroendoscope was introduced into the anterior horn of the lateral ventricle through a unilateral precoronal burr hole. In cases of third ventricular extension, the cystic wall could be seen through the foramen of Monro, so it was perforated with forceps or an ME2 monopolar cutting tool (Codman & Shurtleff, Raynham, Massachusetts, USA). In cases of hypothalamic extension, the third ventricular wall bulged due to compression by the cyst, so the cyst was perforated with forceps through the thinning lateral wall of the third ventricle. The inside of the cyst was irrigated with artificial spinal fluid (ARTCEREB Irrigation and Perfusion Solution for Cerebrospinal Surgery; Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan) to drain the cyst contents. The area that adhered to the wall of the third ventricle was dissected with forceps to the extent possible. Because simple perforation alone could lead to re-occlusion of the fistula, the cyst wall was partially resected to the extent possible in the free area. If the base of the third ventricle or the cyst wall was thin, contralateral cyst wall fenestration was performed to allow communication between the cyst and the subarachnoid space. In cases of hypothalamic extension, extensive cyst wall resection was not performed to avoid causing hypothalamic injury (Figs. 3 and 4). In only two early cases, an Ommaya reservoir was placed for puncture aspiration at the time of tumor re-enlargement.

Statistical analysis

Continuous data are summarized as the mean ± standard deviation in the case of a normal distribution and as the range and median in the case of a nonnormal distribution, as determined using the Shapiro–Wilk test. With respect to the association of ECPR with postoperative hypopituitarism and retreatment because of tumor regrowth, we compared the following data: the maximum tumor diameter; calcification on CT; whether the tumor was monocystic or multicystic; solid component; whether the tumor extended into the third ventricle or into the hypothalamus; whether the patient had undergone previous treatment; whether the contralateral cyst wall fenestration was performed to allow communication between the cyst and subarachnoid space; whether extensive cyst wall resection could be performed; and extensive cyst wall detachment from the wall of the third ventricle. To compare postoperative hypopituitarism, Student's t test or Mann–Whitney's U test was used for continuous data, and Fisher's exact test was used for categorical data. For the retreatment comparison, after the maximum tumor size was divided into two groups (≥ 26 mm and < 26 mm) using a ROC analysis, each item was compared using the log-rank test in the period from SRT to retreatment. In addition, the risk ratio of hypopituitarism due to ECPR and the hazard ratio of retreatment after SRT were analyzed by logistic regression analysis and Cox regression analysis using the forward–backward stepwise method. SPSS ver. 21 was used for the statistical analysis.

Results

Patient selection

There were 34 cases of craniopharyngioma treated with ECPR at Toranomon Hospital. During the same period, 270 were transsphenoidal surgeries performed for craniopharyngioma (two of which were cases of regrowth after neuroendoscopy) [39, 40]; thus, ECPR accounted for approximately 11.2% of all craniopharyngioma surgeries. Nine of the 34 patients were excluded because they underwent ECPR without SRT prior to extended transsphenoidal surgery due to obstructive hydrocephalus or the formation of large cysts. Six patients underwent ECPR only without postoperative SRT. One of the six patients did not complete the follow-up after undergoing ECPR because of a poor general condition;

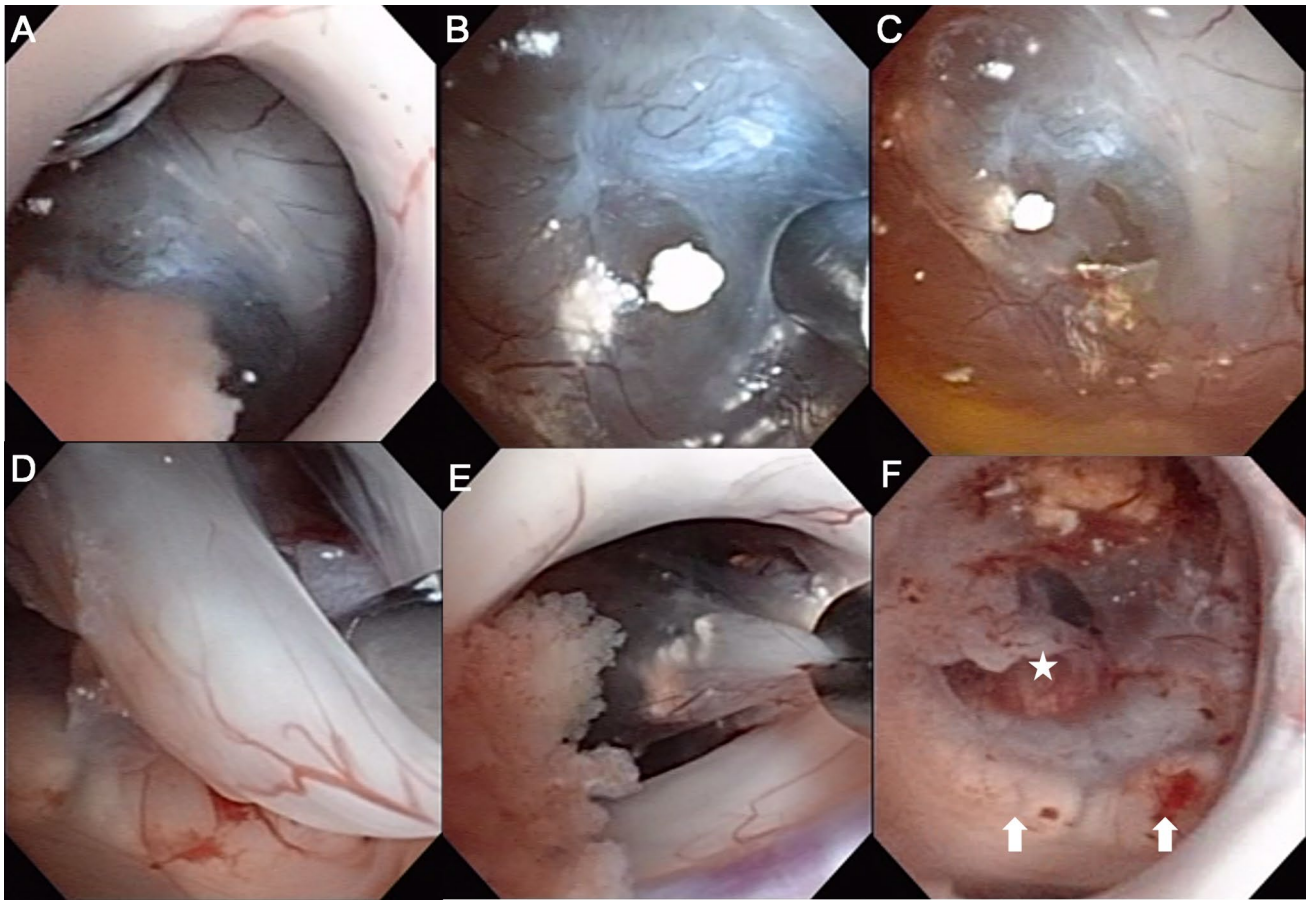

Fig. 3 Intraoperative findings of a case with third ventricular extension. **A** The cyst was observed through the foramen of Monro. **B**: The cyst wall was perforated with forceps. **C** The cyst shrank in the third ventricle after perforation. **D** The cyst wall was dissected from the lateral wall of the third ventricle. **E** The cyst wall was resected using forceps. **F** View after extensive cyst wall resection. The star indicates the third ventriculostomy, and the arrows indicate the mammillary bodies

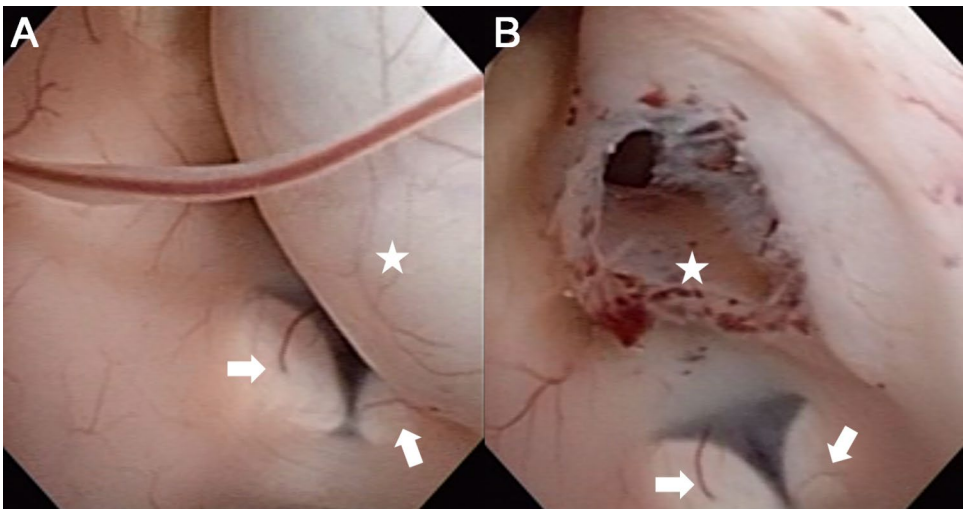

Fig. 4 Intraoperative findings of a case with hypothalamic extension. **A** The star indicates the lateral wall of the third ventricle compressed by the cyst extending into the hypothalamus. The stars indicate the mammillary bodies. **B** The star indicates perforation of the cyst covered with the left lateral wall of the third ventricle. The stars indicate the mammillary bodies

therefore, this patient was excluded from the study. Five of the six patients were early cases of craniopharyngioma treated with ECPR. SRT was not performed at that time, and all patients experienced tumor recurrence. Consequently, SRT was incorporated into the treatment regimen, and five of these patients underwent re-treatment for tumor regrowth

11 to 60 months after initial ECPR (Fig. 2). Two of five patients were excluded because they underwent extended transsphenoidal surgery after tumor regrowth. The other two of the five patients were included in this study because they underwent a second ECPR procedure and postoperative SRT. The remaining one of five patients was also included in this study because he underwent SRT due to slight tumor re-enlargement during the 46 months of follow-up after ECPR. Thus, since all five initial patients treated with ECPR alone had recurrence, SRT was added thereafter (Fig. 2). Finally, 22 patients who underwent SRT after regrowth were included in this study (Fig. 1).

Demographics

The patient characteristics before ECPR are summarized in Table 1. Among the 22 patients, there were 12 males and 10 females, with an average age of 59.0 ± 13.7 years old (range: 32 – 84 years old). One patient had previously undergone craniotomy at another hospital. One patient had previously undergone craniotomy and postoperative local irradiation at another hospital. Thirteen patients (59%) had visual field deficits; of them, one recurrent patient also had oculomotor deficits due to a previous craniotomy. Nine patients (41%) had memory disturbance due to hydrocephalus in eight cases and hypothalamic compression by the tumor in one case. Anterior pituitary function was normal in 14 patients (64%), seven patients (32%) had partial hypopituitarism, and one patient (4.5%) had panhypopituitarism. There were no cases of preoperative diabetes insipidus. The maximum tumor diameter was 19 – 56 mm (median, 30 mm). The pituitary stalk was the preinfundibular type in four patients (13%), the transinfundibular type in 13 patients (59%) and the retroinfundibular type in five patients (23%) [16]. In four cases (18%), the tumor was polycystic; however, all cysts were accessible by neuroendoscopy. In six cases (27%), tumors had a solid component that was not more than 5% of the total tumor volume. In seventeen cases (77%), the tumor extended to the third ventricle. In five cases (23%), the tumor extended to the hypothalamus from the suprasellar region and compressed the third ventricle from the lateral side (Fig. 5). Seventeen patients (77%) showed calcification on head CT. Regarding the pathological subtype, 14 (64%) were adamantinomatous-type, and five (23%) were papillary-type. In three cases (14%), the pathological subtype could not be diagnosed because the specimen size was insufficient for the diagnosis.

Table 1 Characteristics of 22 patients who underwent ECP

Sex	Male	12
	Female	10
Age (years)		59.0 ± 13.7
Previous treatment	+	4
	-	18
Visual disturbance	+	13
	-	9
Anterior pituitary function	Normal	14
	Partial hypopituitarism	7
	Panhypopituitarism	1
Diabetes insipidus	+	0
	-	22
Memory disturbance	+	9
	-	13
Obstructive hydrocephalus	+	8
	-	14
Maximum tumor diameter (mm)		19–56 (median: 30 mm)
Multicystic	+	4
	-	18
Solid component	+	6
	-	16
Tumor extension	Third ventricle	17
	Hypothalamus	5
Calcification on CT	+	17
	-	5
Pathological subtype	Adamantinomatous	14
	Papillary	5
	Undetermined	3

Outcomes of ECPR

ECPR was safely performed, and cyst shrinkage was accomplished in all cases. Third ventriculostomy through the cyst wall or contralateral cyst wall fenestration was performed in 10 cases (45%). Extensive cyst wall detachment from the wall of the third ventricle was performed in six cases (27%). Extensive cyst wall resection was performed in 11 cases (50%).

Thirteen of the 22 patients had visual dysfunction and nine did not. In 12 of 13 patients (92%) with visual field disturbance, visual function improved immediately after ECPR; in the remaining case, which was a case of recurrence, the patient had previously undergone craniotomy at another hospital, and the visual field disturbance had continued from the previous surgery. In this patient, the visual field deficit did not deteriorate after ECPR, and the newly arising oculomotor disturbance improved after ECPR. There was no postoperative deterioration of visual function in the nine patients who did not have visual field disturbances before ECPR.

Overall, pituitary function was unchanged after ECPR in 14 patients (64%) and deteriorated in eight patients (36%). Among the 14 patients with normal pituitary function before ECPR, pituitary function remained normal in 11 (79%) and

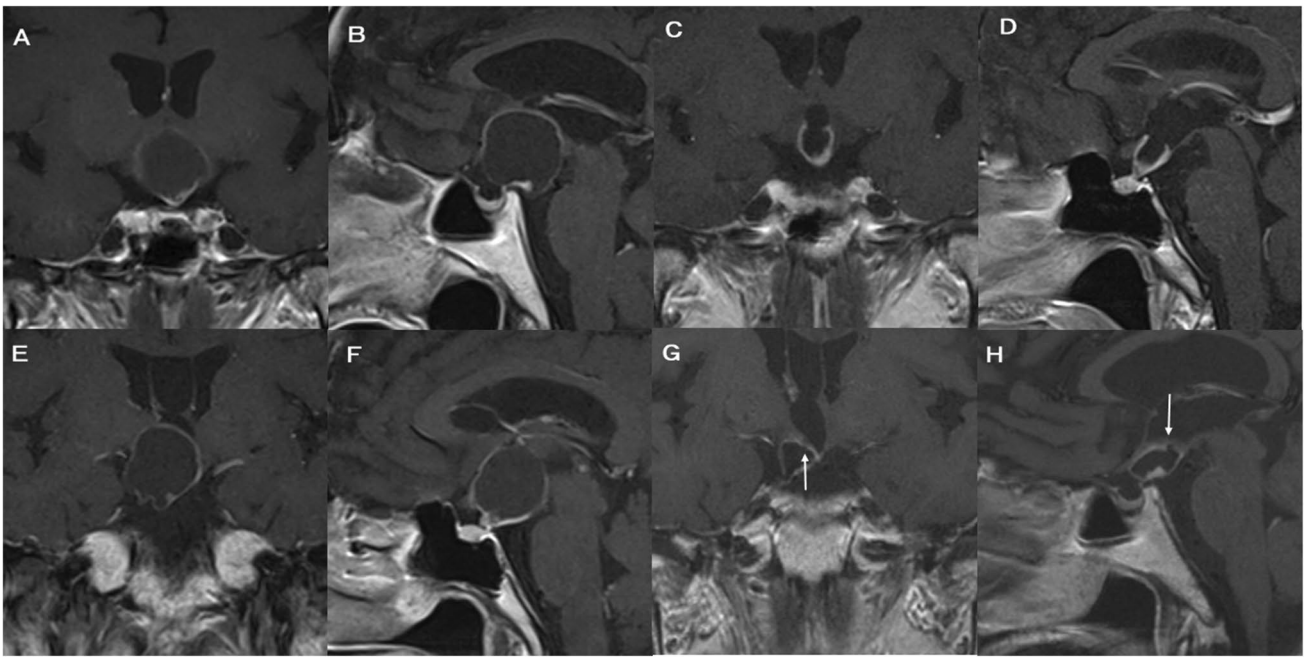

Fig. 5 Pre- and postoperative contrast T1-weighted images from a case with third ventricular extension and a case with hypothalamic extension. **A** – **D**: A case with third ventricular extension. **A**: Preoperative coronal section. **B**: Preoperative sagittal section. **C**: Postoperative coronal section. **D**: Postoperative sagittal section. **E** – **H**: A case with hypothalamic extension. **E**: Preoperative coronal section. The third ventricle is compressed along with the right lateral wall by the cyst. F: Preoperative sagittal section. **G**: Postoperative coronal section. The floor of the third ventricle is preserved. The arrow indicates the fenestration point. **H**: Postoperative sagittal section. The arrow indicates the fenestration point

deteriorated to partial hypopituitarism in two (14%). One of the 14 patients (7%) developed panhypopituitarism and diabetes insipidus. Among seven patients with partial hypopituitarism before ECPR, pituitary function remained the same as preoperatively in four patients (57%), deteriorated to panhypopituitarism in two patients (29%) and panhypopituitarism and diabetes insipidus in one patient (14%). One patient with panhypopituitarism before ECPR developed diabetes insipidus after ECPR. There was no significant relationship between preoperative hypopituitarism and deterioration of pituitary function after ECPR ($P = 0.62$) (Table 2).

Memory disturbance improved in all nine cases.

As a complication of ECPR, one patient developed meningitis due to wound infection. Hypothalamic injury and postoperative chemical meningitis were not observed in any of the patients.

Outcomes of SRT

In this study, 18 of 22 patients (82%) achieved tumor control without further treatment 19 – 87 months (median, 33 months) after SRT (Fig. 2, 6). SRT was performed between 0 – 46 months following ECPR, and all but one patients received SRT within 0 – 5 months. The prescribed marginal doses were 18 – 30 Gy (median, 28 Gy) in 3 – 10 fractions (median, 7 fractions). Of the 18 patients whose tumor were controlled, two elderly patients died from other diseases at 19 and 28 months after SRT. As a result, The Ommaya reservoirs that were placed in two patients had never been used. Three patients experienced transient cyst enlargement on MRI at 5, 10, and 14 months after SRT, which later spontaneously shrank. Hypopituitarism was observed as an adverse event in two of 18 patients (11%) whose tumors were controlled.

Four of the 22 patients (18%) showed cyst enlargement that required additional treatment after SRT. One of these four patients had previously undergone craniotomy and radiotherapy at another hospital, as mentioned above; small cysts appeared at 33 and 50 months after SRT, so additional SRT was performed again to reduce the cysts. The remaining three patients underwent extended transsphenoidal surgery at nine, nine, and 14 months because the cyst continued to grow after SRT. The visual field defects that had once improved after ECPR deteriorated, and the visual field defects remained after the extended transsphenoidal surgery. In particular, the two patients who underwent surgery at nine months showed cyst enlargement even in the two months between ECPR and SRT.

Table 2 Factors associated with postoperative hypopituitarism

		Postoperative deterioration of pituitary function			Logistic regression analysis	
		+	-	*P*	Odds ratio (95% CI)	*P*
		(*n* = 6)	(*n* = 16)			
Preoperative hypopituitarism	+	11	5	0.62		
	-	3	3			
Maximum tumor diameter (mm)		28.3 ± 6.7	32.3 ± 11.3	0.43		
Calcification on head CT	+	5	12	0.58		
	-	1	4			
Multicystic	+	1	3	0.71		
	-	5	13			
Solid component	+	1	5	0.46		
	-	5	11			
Tumor extension	Third ventricle	6	11	0.17		
	Hypothalamus	0	5			
Previous treatment	+	0	4	0.25		
	-	12	6			
Communication to the subarachnoid space	+	2	8	0.42		
	-	4	8			
Extensive resection of the cyst wall	+	5	6	0.074		
	-	1	10			
Extensive detachment from lateral wall of the third ventricle	+	4	2	0.025	14.0 (1.47–133.2)	0.022
	-	2	14		1	

Postoperative pituitary function was more likely to deteriorate when the cyst wall was extensively dissected from the lateral wall of the third ventricle

Factors associated with postoperative hypopituitarism and retreatment

We examined the association of postoperative deterioration of pituitary function and retreatment with the maximum tumor diameter, the presence of calcification on CT, mono- or multicystic, the presence of the solid component, third ventricular or hypothalamic tumor extension, previous treatment, extensive cyst wall resection during ECPR, communication with the subarachnoid space by contralateral cyst wall fenestration, and extensive detachment from the ventricular wall. The results showed that postoperative pituitary function was significantly more likely to deteriorate in cases of extensive detachment from the ventricular wall ($P = 0.025$). The odds ratio of deterioration of pituitary function with tumor capsule detachment from the ventricular wall using logistic regression analysis was 14.0 ($P = 0.022$, 95% CI: 1.47–133.2) (Table 2). Regarding the association between retreatment and the above items, retreatment was significantly more likely in cases of hypothalamic extension ($P = 0.014$) (Table 3). The hazard ratio of retreatment with hypothalamic extension and compression of the third ventricle from the lateral side using Cox regression analysis was 9.9 ($P = 0.048$, 95% CI: 1.03 – 95.8) (Table 3).

Discussion

Outcomes of combined treatment with ECPR and SRT

Our case series shows that ECPR for cystic craniopharyngioma is a minimally invasive procedure aimed at preserving pituitary function that resulted in improvement of visual function in most cases and preservation of pituitary function in two-thirds of cases. Hypothalamic injury and serious complications were absent. If extended transsphenoidal surgery can achieve both curative resection and functional preservation, it is the best option. However, especially in cases of retroinfundibular or transinfundibular craniopharyngioma, partial tumor resection may be necessary to preserve pituitary function [11, 39, 40]. Although we reported that preservation of the hypothalamus was compatible with total resection even by extended transsphenoidal surgery, there was a high risk of hypopituitarism and diabetes insipidus when total resection was performed [39, 40]. Therefore, if long-term tumor control can be achieved, this combination therapy, which is minimally invasive and provides a higher rate of functional preservation than extended transsphenoidal surgery, seems to be a reasonable option.

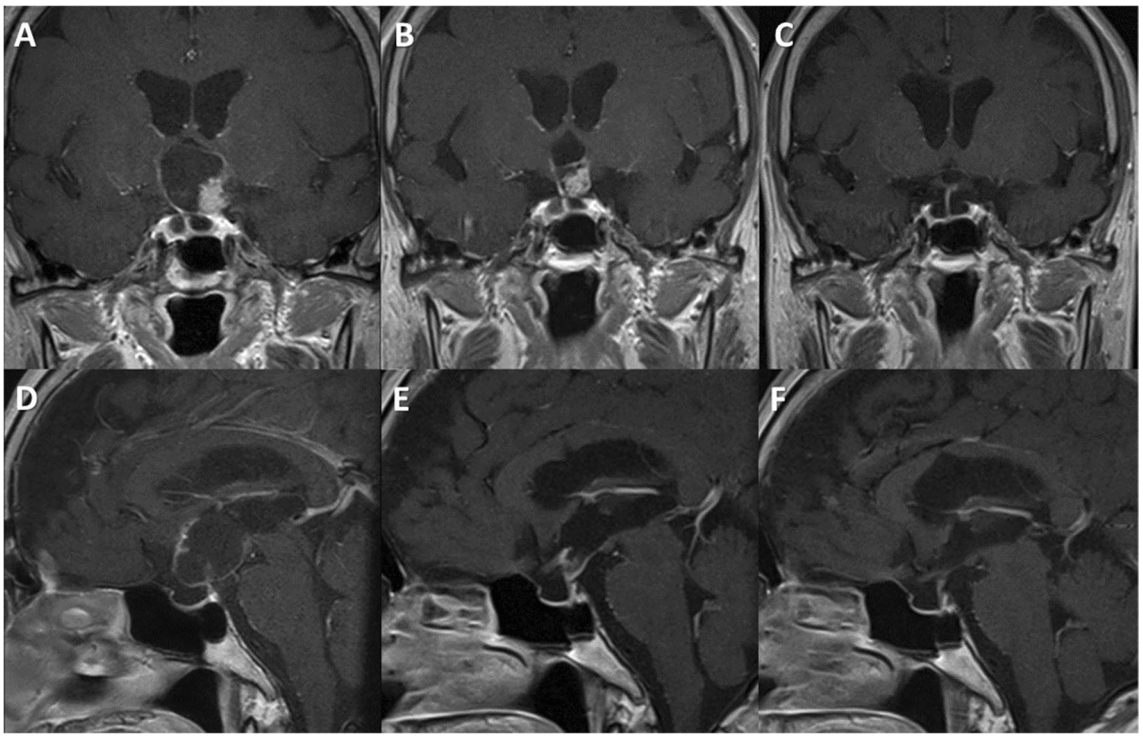

Fig. 6 Contrast-enhanced magnetic resonance imaging of a representative case of craniopharyngioma controlled by neuroendoscopic cyst partial resection and stereotactic radiotherapy. **A**, **B**, **C**: Coronal section. **D**, **E**, **F**: Sagittal section. **A**, **D**: Before neuroendoscopic cyst partial resection (ECPR). **B**, **E**: After ECPR. **C**, **F**: 33 months after stereotactic radiotherapy (SRT). This patient was a 69-year-old woman. She had visual impairment and was diagnosed with suprasellar craniopharyngioma. Her preoperative pituitary function was normal. After ECPR, her visual disturbance improved, and her pituitary function did not deteriorate. After SRT, the tumor shrank further and showed no regrowth for 33 months after SRT

Craniopharyngiomas are highly prone to local recurrence following partial resection alone, resulting in recurrence in 45% of cases [7]. On the other hand, the radiosensitivity of these tumors is high, and SRT has been reported to provide tumor control at rates of 62 – 100%, with no difference in recurrence rate between total resection and subtotal resection followed by SRT [5, 7]. In our study, all five patients without SRT showed recurrence after the initial follow-up, so SRT after ECPR was considered essential. However, tumor control was obtained in 82% of all cases with a combination of ECPR and SRT. Takano et al. also reported 89% tumor control with a similar method [37]. Adding SRT after ECPR markedly improves tumor control rates. However, craniopharyngiomas may recur in the long term even after complete surgical removal. Our median follow-up of 33 months may not be sufficient to evaluate the long-term outcome of this treatment, and longer follow-up may be necessary because one of the patients who recurred had new cyst formation at 33 and 50 months after SRT. However, Takano et al. reported similar results with a longer median follow-up of 72.9 months. Therefore, sufficient long-term tumor control can be expected in our case.

Indications for combined treatment with ECPR and SRT

One of the reasons for the favorable therapeutic outcome regarding tumor control is that this procedure was limited to only optimal cases for neuroendoscopic surgery based on the tumor shape and the direction of progression. Since the purpose of this procedure is pretreatment for volume reduction before SRT, this procedure is not applied in cases with a large proportion of solid components. If the tumor volume is large before SRT, then there is a risk of radiation-induced optic neuropathy and even hypothalamic damage. In this study, solid components were not more than 5% of tumor volume in all cases. In addition, all cysts should be accessible by neuroendoscopy, even in cases of multicystic craniopharyngioma, to prevent regrowth after SRT.

The results of this study indicate that craniopharyngiomas with extension into the hypothalamus and compression of the third ventricle from the lateral side are more likely to require retreatment than patients with direct extension into the third ventricle. Therefore, treatment outcomes may become worse if the indication is expanded. However, craniopharyngiomas are cystic and extend to the third ventricle in

Table 3 Factors associated with retreatment after stereotactic radiotherapy

			Log-rank test			Cox regression analysis	
Retreatment							
		n	+	-	*P*	Hazard ratio (95% CI)	*P*
Maximum tumor diameter (mm)	≥ 26 mm	12	1	11	0.9		
	< 26 mm	10	3	7			
Calcification on head CT	+	17	4	13	0.29		
	-	5	0	5			
Multicystic	+	4	1	3	0.85		
	-	18	3	15			
Solid component		6	0	6	0.2		
		16	4	12			
Tumor extension	Third ventricle	17	1	16	0.014	1	
	Hypothalamus	5	3	2		9.9 (1.03–95.8)	0.048
Previous treatment	+	4	1	3	0.99		
	-	18	3	15			
Communication to the subarachnoid space	+	2	8	10	0.9		
	-	2	10	12			
Extensive resection of the cyst wall	+	1	10	11	0.42		
	-	3	8	11			
Extensive detachment from lateral wall of the third ventricle	+	0	6	6	0.27		
	-	4	12	16			

Craniopharyngiomas that extended into the third ventricle were less likely to need retreatment, while those that extended into the hypothalamus and compressed the third ventricle from the lateral side were more likely to need retreatment

many cases. Furthermore, although we previously reported that third ventricular craniopharyngiomas can also be removed by extended sphenoidal surgery [25], ECPR may replace this procedure in cases of purely cystic third ventricular craniopharyngiomas. On the other hand, in cases which do not directly extend into the third ventricle, suprasellar blood vessels or nerves may be interposed between the tumor capsule and the hypothalamus. Therefore, extended transsphenoidal surgery or other skull base surgery may be preferable because there are risks of injury to these vital structures and results of SRT were not good.

This combination therapy requires radiation, which can cause side effects such as pituitary dysfunction, hypothalamic disorders, and secondary tumor, so it may not be particularly recommended for pediatric patients. Therefore, we initially adopted this procedure for elderly patients. However, no patients suffered from such side effects of SRT during the follow-up, so we gradually expanded the indication to include younger patients. Most pediatric craniopharyngiomas are treated with radiation therapy when the tumor remains after surgery. In particular, total tumor removal may be complicated by hypothalamic injury and endocrine disorders, and radiation therapy is reported to be used in combination with partial tumor removal to preserve these functions [12, 17, 32]. It was previously reported that the need for hormone replacement after CyberKnife for craniopharyngioma was as low as 2% [15]. In particular, patients who had not received hormone replacement prior to SRT did not experience functional decline after treatment. Therefore, this combination therapy with ECPR and SRT may also be indicated for younger patients to preserve pituitary function.

In cases of panhypopituitarism with diabetes insipidus, extended transsphenoidal surgery may be prioritized for curability [39, 40]. However, there was no relationship between preoperative partial hypopituitarism and postoperative deterioration of pituitary function in this study. Therefore, this procedure may also be indicated for patients with partial hypopituitarism if it is beneficial when compared with the advantages of radical cure and preservation of residual pituitary function. Traditional approaches, including transsphenoidal and transcranial surgery, have been the mainstay treatment options. These methods offer the potential benefit of immediate and complete tumor removal. However, these methods also carry significant risks of postoperative complications, such as hypothalamic injury, hypopituitarism, diabetes insipidus and cerebrospinal fluid leakage, particularly when aiming for gross total resection. As mentioned above, it was reported that there were no difference in the recurrence rate of craniopharyngioma between total resection and subtotal resection followed by SRT, so in recent years, "hypothalamus-sparing surgery" is performed to preserve the hypothalamus and endocrine function[28]. However, a

recent meta-analysis still reports a lower recurrence rate for total resection[1]. It has also been reported that significant dysfunction of the anterior and posterior pituitary often ensues, although preservation of the pituitary stalk reduces the rate of postoperative endocrinopathy[27]. If the tumor recurs after SRT, whether after ECPR or after subtotal resection, direct surgery is necessary. However, reoperation after ECPR is expected to be easier than after partial resection because the suprasellar anatomy is preserved. This combination therapy with ECPR and SRT is not a replacement for direct surgery, but may result in long-term tumor control. Therefore, it may be considered as an additional treatment option prior to direct surgery for cystic craniopharyngiomas in which pituitary function is preserved.

Recent reports have shown the effectiveness of BRAF/MEK inhibitors in treating papillary craniopharyngioma [3]. In the future, drug therapy may be a viable treatment option for papillary craniopharyngiomas once a pathological diagnosis is made, potentially eliminating the need for SRT. However, SRT still offers some advantages in terms of health economics.

Procedure for ECPR

Since it is difficult to achieve a radical cure by ECPR alone, complications of ECPR must be minimized. In this study, the only complication directly related to ECPR was meningitis following wound infection in one case, except for pituitary dysfunction. However, postoperative pituitary function deterioration occurred in 36% of the patients in the present study. In cases of pituitary dysfunction caused by ECPR, there were also strong bilateral hypothalamic adhesions, and the dysfunction was more likely to be exacerbated when these adhesions were dissected. Because extensive cyst wall resection or extensive detachment did not always prevent recurrence, it would be better to limit detachment of the cyst wall from the ventricular wall to an area that can be easily dissected to preserve pituitary function. ECPR is not intended for aggressive surgical removal, but only as a pre-treatment of SRT. The purpose of ECPR is to decrease the target volume of SRT by perforating the cystic tumor and to prevent re-occlusion before SRT by partial resection. Therefore, for more aggressive tumor removal that requires surgical micromanipulation, skull base surgery such as extended transsphenoidal surgery is preferable. However, this combination therapy is not intended for that purpose. It is crucial to prioritize the prevention of hypopituitarism and other complications over increasing the tumor removal rate.

Timing of retreatment after SRT

Craniopharyngiomas have been reported to transiently increase in size until 4.27 to 9.5 months after SRT and then shrink [18, 35]. However, if there is no tendency toward shrinkage after 6 months to 1 year, then direct surgery should be performed. Especially in the cases of three patients who underwent extended transsphenoidal surgery due to regrowth after SRT, the visual field deficit remained a sequela, so it may be better to perform surgery early if the visual field deficit has progressed. Moreover, SRT should be performed early after ECPR, since in our study, two patients who required reoperation due to regrowth after SRT showed enlargement between ECPR and SRT.

Conclusions

In selected cases with predominantly cystic craniopharyngioma extending to the third ventricle, the ECPR combined with SRT is an alternative therapeutic strategy to the endoscopic endonasal radical surgery in terms of preservation of pituitary function and surgical complication. It should be noted that excessive detachment of the cyst wall from the hypothalamus should be avoided in order to preserve pituitary function with a higher probability.

Funding This study was not funded by any specific grant.

Data availability The datasets generated and/or analyzed in the current study are not publicly available due to ethical approval conditions, but are available from the corresponding author upon reasonable request.

Declarations

Ethics approval This retrospective study was approved by the Clinical Research Ethics Review Committee of Toranomon Hospital (No. 1748).

Competing interests The authors declare they have no conflicts of interest, no commercial relationships and received no support from pharmaceutical or other companies.

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