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Differences in Treatment Outcomes Depending on the Adjuvant Treatment Modality in Craniopharyngioma

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Purpose: Adjuvant treatment for craniopharyngioma after surgery is controversial. Adjuvant external beam radiation therapy (EBRT) can increase the risk of long-term sequelae. Stereotactic radiosurgery (SRS) is used to reduce treatment-related toxicity. In this study, we compared the treatment outcomes and toxicities of adjuvant therapies for craniopharyngioma.

Materials and Methods: We analyzed patients who underwent craniopharyngioma tumor removal between 2000 and 2017. Of the 153 patients, 27 and 20 received adjuvant fractionated EBRT and SRS, respectively. We compared the local control (LC), progression-free survival (PFS), and overall survival between groups that received adjuvant fractionated EBRT, SRS, and surveillance.

Results: The median follow-up period was 77.7 months. For SRS and surveillance, the 10-year LC was 57.2% and 57.4%, respectively. No local progression was observed after adjuvant fractionated EBRT. One patient in the adjuvant fractionated EBRT group died owing to glioma 94 months after receiving radiotherapy (10-year PFS: 80%). The 10-year PFS was 43.6% and 50.7% in the SRS and surveillance groups, respectively. The treatment outcomes significantly differed according to adjuvant treatment in non-gross total resection (GTR) patients. Additional treatment-related toxicity was comparable in the adjuvant fractionated EBRT and other groups.

Conclusion: Adjuvant fractionated EBRT could be effective in controlling local failure, especially in patients with non-GTR, while maintaining acceptable treatment-related toxicity.

Key Words: Fractionated radiotherapy, stereotactic radiosurgery, craniopharyngioma, local control, progression-free survival

INTRODUCTION

Craniopharyngioma is a rare intracranial tumor that frequently presents with symptoms such as visual loss and endocrine disturbance.[1,2] Surgery is the mainstay of treatment for this type of tumor; however, craniopharyngiomas often recur and cause severe morbidity.[3,4] Although the associated treatment outcome is favorable, complete tumor removal is often challenging owing to the presence of nearby structures, as craniopharyngiomas are usually located at the suprasellar region. Craniopharyngiomas represent about 2% of intracranial tumors and cause displacement of cranial nerves and optic chiasms. Aggressive resection can lead to favorable treatment outcomes; however, it can also increase treatment-related side effects, such as visual impairment and endocrine complications.[3,5,6]

Partial excision followed by adjuvant radiotherapy (RT) in patients with craniopharyngioma has demonstrated a 10-year progression-free survival (PFS) of 75%–85%, accompanied by the risk of radiation optic neuropathy, endocrine deficiency, or neurological complications.[7-9] Due to the increased risk of treatment-related toxicity, stereotactic radiosurgery (SRS) has gained

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increasing attention. SRS and external beam radiation therapy (EBRT) have been used as adjuvant RT modalities for residual or recurrent tumors after surgery. Although several studies have assessed the effectiveness of SRS or EBRT in craniopharyngioma,[10-13] no studies have evaluated the appropriate adjuvant treatment modality for tumor control and maintenance of visual and endocrine function.

In this study, we aimed to analyze the role of adjuvant EBRT in craniopharyngiomas. We also investigated the treatment-related toxicities of adjuvant therapies in patients with craniopharyngioma.

MATERIALS AND METHODS

Study population

We collected data on patients diagnosed with craniopharyngioma between 2000 and 2017 at Severance Hospital. A total of 153 patients underwent tumor removal for craniopharyngioma. Adjuvant treatment was decided following a multi-disciplinary discussion at the neuro-oncology conference. Adjuvant RT was performed in cases where residual tumor remained after resection, or where there was a risk of recurrence even after total resection due to high volume of tumor or cystic component of crainopharyngioma. When the tumor was completely removed with no risk of recurrence, the patients underwent surveillance without adjuvant treatment. SRS has been performed on small, discrete tumors and in young children, while EBRT was applied to patients with larger tumors. In cases where SRS was difficult to perform, fractionated EBRT was administered. Patients who received RT or craniotomy for diseases other than craniopharyngioma were not included. Moreover, patients with a follow-up period of less than 6 months were excluded from this study. This study was approved by the Institutional Review Board of Severance Hospital in accordance with the Declarations of Helsinki (4-2018-1041). Consent was waived due to the retrospective nature of the study, and the waiver of consent was approved by the Institutional Review Board of Severance Hospital.

Surgery and assessment of surgical resection

All patients underwent maximum surgical resection via craniotomy or the trans-sphenoid approach (TSA). The extent of tumor resection was judged to be gross total resection (GTR) when the following criteria were met: 1) no remnant of the tumor was observed on immediate postoperative magnetic resonance imaging (MRI) and 2) no tumor was observed on intraoperative inspection.[14] Experienced neurosurgeons evaluated near-total resection (NTR) and partial resections (PR), while neuroradiologists reviewed MRI findings. NTR was defined as remnant membrane or residual tumor area <1.5 cm^2, while subtotal resection (STR) was defined as a volumetric diminishment of more than 90% and residual tumor area of ≥1.5 cm^2. PR was defined as a volumetric diminishment of <90%. We performed a postoperative MRI within 48 h of the operation. TSA was performed in patients with the following criteria: 1) tumor mass did not extend laterally beyond the course of the internal carotid artery; 2) patients had a prefixed optic chiasm; and 3) tumor mass was mainly localized either posterior to the interpeduncular cistern or superior to the third ventricle.[14]

RT

Patients who received adjuvant fractionated EBRT were immobilized using an individually customized thermoplastic mask. A computed tomography (CT) scan was performed with a 3-mm slice thickness for treatment planning. The target volume was defined using stereotactically guided image fusion with preoperative and postoperative MRI scans. The gross target volume (GTV) included the tumor bed and gross volume of the remnant tumor in patients with residual tumors. The GTV included contrast-enhancing solid lesions and cystic components of the tumor using MRI scans. The clinical target volume (CTV) was expanded by 5–10 mm, above the GTV and tumor bed volume, prior to surgery. The planning target volume included the CTV with an additional 3–5 mm margin in all directions to compensate for the uncertainty in the positioning of patients. The target was delineated using either the Pinnacle (Philips Healthcare, Andover, MA, USA) or MIM software (MIM Software, Inc., Cleveland, OH, USA).

Fractionated EBRT was delivered in conventional fractionation to a total dose ranging from 45 Gy to 60 Gy, with a median dose of 54 Gy. Of the 27 patients, 22 received fractionated EBRT with intensity-modulated radiotherapy (IMRT), while five patients were treated using three-dimension conformal radiotherapy (3D-CRT). In the SRS group, the median radiation dose delivered was 14 Gy, ranging from 9 Gy to 20 Gy.

The beam arrangements for 3D-CRT usually consisted of 3–5 non-coplanar beams with 6 megavoltage energy photons. IMRT was performed using either Tomotherapy (Accuray Inc., Sunnyvale, CA, USA) or Elekta volumetric modulated arc therapy (VMAT) (Elekta, Stockholm, Sweden). For the 3D-CRT plan, the Pinnacle (Philips Radiation Oncology Systems, Milpitas, CA, USA) system was used, whereas the Tomotherapy radiation treatment planning system (Accuray Inc., Sunnyvale, CA, USA) was used for Tomotherapy. In the case of VMAT, the RayStation (RaySearch Laboratories AB, Stockholm, Sweden) system was used for RT planning.

SRS was performed using a Leksell Gamma Knife (Elekta, Stockholm, Sweden). A Leksell stereotactic frame was used for immobilization. The target was defined as the residual tumor identified through gadolinium-enhanced T1-weighted three-dimensional MR images after surgery. GammaPlan software (Elekta) was used for dose planning. A 50% isodose at the target margin was prescribed for the treatment. The visual pathways nearby the target volume were included in the 30% prescribed isodose line [15] to preserve visual pathways adjacent

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to the tumor margin. In cases where it was challenging to align the visual pathway with the 30% isodose line, we followed the organs at risk constraints outlined in the QUANTEC guidelines. Examples of fractionated EBRT and SRS are presented in Supplementary Fig. 1 (only online).

Follow-up after treatment

Follow-up MRI scans were obtained at 1, 2, 3, 6, and 8 years after treatment. All patients underwent assessments of endocrine and ophthalmological functions before and after surgery. For endocrinological evaluation, patients visited an endocrinologist every 6 months during the first year and every 2 years thereafter. A combined pituitary function test was used to evaluate pituitary function. All patients underwent ophthalmological assessments before, immediately after, and 6 months after surgery. Ophthalmologic function evaluations were performed depending on the patients' visual acuity.

Statistical analysis

The primary endpoint for this study was the local control (LC). The secondary endpoints were PFS and overall survival (OS). Infield failure of adjuvant fractionated EBRT group was defined as progression of disease within the CTV,[15] while marginal failure was defined as progression of disease outside the CTV and within 10 mm of the CTV. For the adjuvant SRS group, infield failure was defined as disease progression within the surgical cavity, while marginal failure was defined as disease progression within 10 mm outside the surgical cavity. Treatment-related toxicities were compared between the different groups. The time to local failure was defined as the period from the surgery date to the date of the first local progression or last follow-up. PFS was calculated from the surgery date to the date of the last follow-up, death, or disease progression. OS was defined as the time from the date of surgery to death or last follow-up. LC, PFS, and OS were evaluated using the Kaplan–Meier method. Comparisons of groups were performed using analysis of variance for continuous variables and Pearson's chi-square test for categorical variables. Univariate and multivariate analyses determined the significant factors associated with LC and PFS using the log-rank and Cox regression analysis models. The analyses were performed using SPSS software (version 25.0; IBM Corp., Armonk, NY, USA).

RESULTS

Characteristics of patients

A total of 153 patients were included in this study. The median age of the patients was 35 years (interquartile range, 14–51 years), and the median tumor diameter was 2.90 cm (interquartile range 2.30–3.80 cm). Of the 153 patients, 73 (47.7%) underwent GTR of the tumor, and 47 (30.7%) received adjuvant RT. Twenty-seven patients received fractionated EBRT, and 20 received SRS. The patient characteristics, according to adjuvant treatment received, are shown in Table 1. The proportion of patients who underwent GTR was higher in the surveillance group. Conversely, the adjuvant RT group included more patients who underwent STR or PR (p<0.001). In

Table 1. Characteristics of Patients

	Total patients (n=153)	Adjuvant fractionated EBRT (n=27)	SRS (n=20)	Surveillance (n=106)	*p* value
Age (yr)	35 (14–51)	37 (21–57)	23 (12–44)	36 (13–52)	0.079
≤35 years	77 (50.3)	13 (48.1)	13 (65.0)	51 (48.1)	0.371
>35 years	76 (49.7)	14 (51.9)	7 (35.0)	55 (51.9)	
Sex					
Male	83 (54.2)	16 (59.3)	15 (75.0)	52 (49.1)	0.087
Female	70 (45.8)	11 (40.7)	5 (25.0)	54 (50.9)	
Tumor size (cm)	2.90 (2.30–3.80)	3.50 (2.30–4.00)	2.83 (2.36–4.08)	2.86 (2.30–3.50)	0.243
≤2.9 cm	76 (50.3)	8 (30.8)	11 (55.0)	57 (54.3)	0.090
>2.9 cm	75 (49.7)	18 (69.2)	9 (45.0)	48 (45.7)	
Extent of resection					
GTR	73 (47.7)	2 (7.4)	0 (0.0)	71 (67.0)	<0.001
NTR	29 (19.0)	5 (18.5)	4 (20.0)	20 (18.9)	
STR	48 (31.4)	19 (70.4)	14 (70.0)	15 (14.2)	
PR	3 (2.0)	1 (3.7)	2 (10.0)	0 (0.0)	
Pathology					
Papillary type	41 (26.8)	10 (37.0)	3 (15.0)	28 (26.4)	0.544
Adamantinous type	112 (73.2)	17 (63.0)	17 (85.0)	78 (73.6)	

EBRT, external beam radiation therapy; SRS, stereotactic radiosurgery; GTR, gross total resection; NTR, near total resection; STR, subtotal resection; PR, partial resection.
Data are presented as median (interquartile range) or n (%).

the fractionated EBRT group, a total of 5400 cGy with 30 fractions was the highest applied radiation dose (n=20, 74.1%), and most of the patients received IMRT (n=22, 81.5%). In the SRS group, most patients received an SRS dose of more than 20 Gy (n=17, 85.0%).

LC and survival outcomes according to adjuvant treatment

The median follow-up period was 77.7 months (interquartile range, 49.43–121.77 months). The 5-year and 10-year OS rates for all patients were 90.8% and 85.5%, respectively. OS did not differ depending on the adjuvant treatment. The 10-year OS rates in the adjuvant fractionated EBRT, SRS, and surveillance groups were 80.0%, 79.3%, and 85.5%, respectively (p=0.201) (Fig. 1A).

The 5-year and 10-year LC were 76.0% and 64.6%, respectively. The LC was significantly different between groups receiving different adjuvant treatments (p=0.005) (5-year LC: 100% vs. 71.5% vs. 70.8%, 10-year LC: 100% vs. 57.2% vs. 57.4% in fractionated EBRT, SRS, and surveillance groups, respectively) (Fig. 1B). The overall 5-year and 10-year PFS rates were 70.0% and 55.5%, respectively. The 5-year PFS rate in the adjuvant fractionated EBRT group was 100%. One patient who underwent adjuvant fractionated EBRT died owing to glioma, 8 years after treatment. The 5-year PFS rate was 60.0% in the SRS group and 64.6% in the surveillance group (p=0.002) (Fig. 1C).

Factors associated with LC were analyzed using the Cox regression analysis model. Adjuvant treatment and extent of resection were significantly associated with LC (Table 2). Adjuvant treatment was found to be a significant factor even in the multivariate analysis. The PFS in the adjuvant fractionated EBRT group was superior to that in the SRS and surveillance groups. In univariate analysis, female sex, GTR, and adjuvant fractionated EBRT were found to be significantly associated with superior PFS. These three factors remained significant in multivariate analysis (Supplementary Table 1, only online).

Patterns of failures and salvage treatments

Among the patients who received fractionated EBRT, none showed progression of disease. Contrarily, seven patients in the SRS group and 35 patients in the surveillance group showed local progression (Supplementary Table 2, only online). Local progression rates differed according to the resection extent in the surveillance group. Patients who underwent GTR and STR showed 18.3% and 73.3% local progression, respectively.

Of the patients treated with SRS after surgery, only one ex-

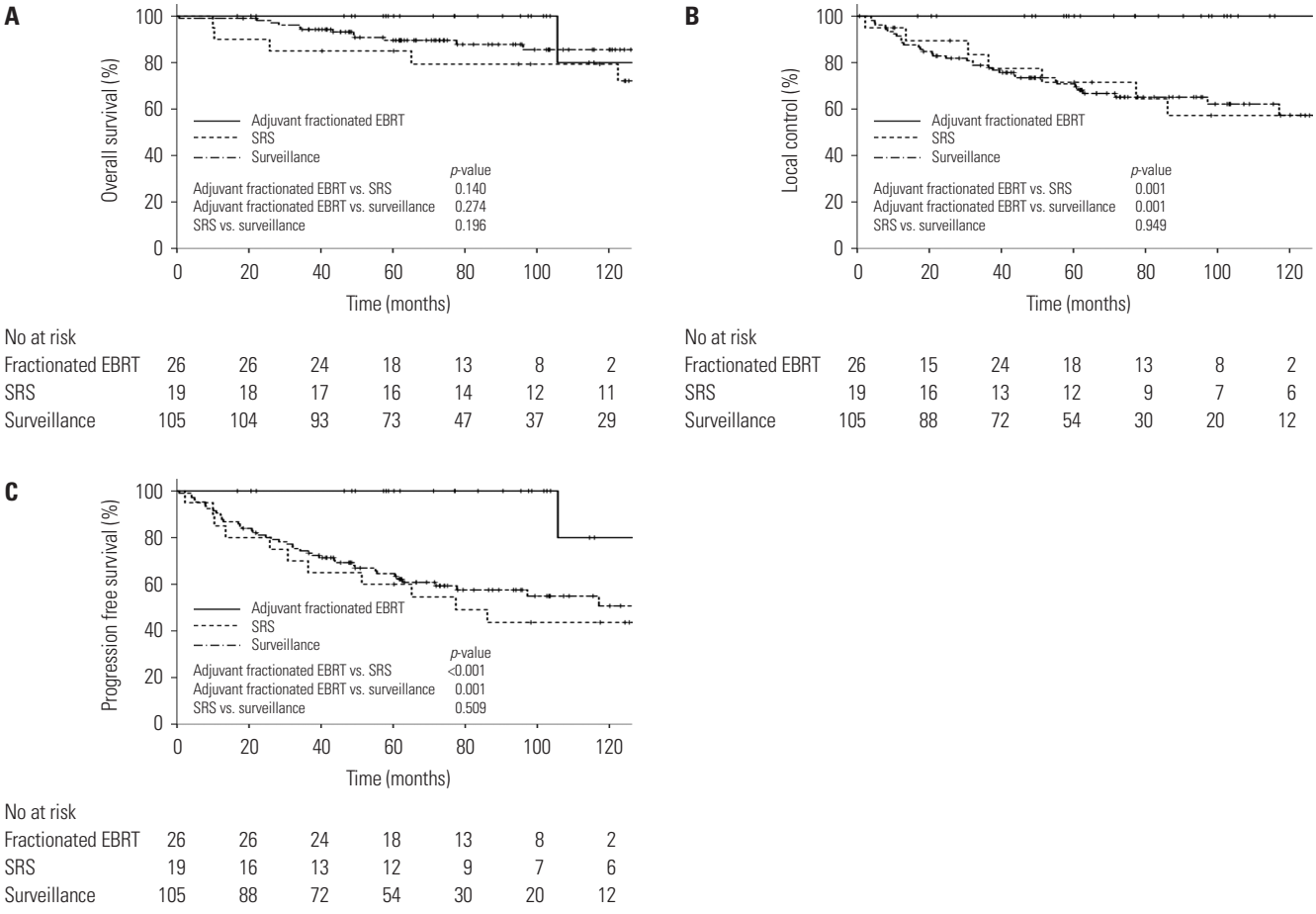

Fig. 1. Comparison of (A) overall survival, (B) local control, and (C) progression-free survival depending on adjuvant treatment. EBRT, external beam radiation therapy; SRS, stereotactic radiosurgery.

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Table 2. Univariate and Multivariate Analyses of Local Control

	Cox univariate analysis			Cox multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age (≤35 years vs. >35 years)	0.66	0.35–1.23	0.190	-	-	-
Sex (male vs. female)	0.62	0.33–1.17	0.142	-	-	-
Tumor size (≤2.9 cm vs. >2.9 cm)	0.91	0.50–1.68	0.772	-	-	-
Pathology (papillary type vs. adamantinous type)	1.14	0.57–2.27	0.713	-	-	-
Extent of resection			0.022			<0.001
GTR vs. NTR	2.64	1.20–5.81	0.016	3.66	1.66–8.05	0.001
GTR vs. STR	1.92	0.91–4.03	0.087	7.45	3.32–16.74	<0.001
GTR vs. PR	6.53	1.47–29.05	0.014	94.45	14.82–602.20	<0.001
Adjuvant treatment			0.005			0.013
Adjuvant fractionated EBRT vs. SRS	3.75	1.25–7.82	0.001	117626.5	NA	0.885
Adjuvant fractionated EBRT vs. surveillance	4.25	1.47–9.46	0.001	460206.5	NA	0.870
Radiation dose (EQD2)	1.00	1.00–1.00	0.096	-	-	-

HR, hazard ratio; CI, confidence interval; GTR, gross total resection; NTR, near total resection; STR, subtotal resection; PR, partial resection; EBRT, external beam radiation therapy; SRS, stereotactic radiosurgery; EQD2, equivalent dose in 2 gy fractions; NA, not applicable.

perienced infield failure, while six experienced marginal failure. The re-operation was mostly performed for salvage treatment in the SRS group (n=6, 85.7%), and SRS was the most common treatment in the surveillance group (n=15, 42.9%). As salvage treatment, fractionated EBRT did not cause any recurrence or progression, while a total of four patients showed recurrence after SRS with or without re-operation (Supplementary Fig. 2, only online).

Treatment outcomes based on surgical extent

The LC was significantly different according to tumor extent. The patients were stratified into two groups: patients who underwent GTR and those who underwent non-GTR, such as NTR, STR, and PR. The LCs of GTR patients were superior to those of non-GTR patients (5-year LC: GTR vs. non-GTR, 84.3% vs. 68.1%) (Fig. 2A). Among the GTR patients, the LC according to adjuvant treatment was analyzed. There was no significant difference in LC according to adjuvant treatment in the GTR group (Fig. 2B). On the contrary, the LC was significantly different depending on adjuvant treatment in the non-GTR group (Fig. 2C). The fractionated EBRT group showed superior LC compared to the SRS and surveillance groups (5-year LC: adjuvant fractionated EBRT vs. SRS vs. surveillance, 100% vs. 71.5% vs. 43.9%).

LC and survival outcomes based on the 2021 World Health Organization (WHO) central nervous system (CNS) classification

We compared the characteristics of patients with papillary craniopharyngioma (PCP) and adamantinomatous craniopharyngioma (ACP) (Supplementary Table 3, only online). Patients with ACP were younger than those with PCP. The tumor size of patients with ACP was larger than that of patients with PCP. The remaining patient characteristics were well-balanced between ACP and PCP.

In patients with PCP, the LC was significantly different according to the adjuvant treatment (Supplementary Fig. 3A, only online). The adjuvant fractionated EBRT group showed superior LC than did the SRS and surveillance groups (5-year LC: adjuvant fractionated EBRT vs. SRS, 100% vs. 33.3%, p=0.011; adjuvant fractionated EBRT vs. surveillance groups 100% vs. 73.7%, p=0.074). Similarly, a difference in LC depending on adjuvant treatment was observed for patients with ACP (Supplementary Fig. 3B, only online). The 5-year LC was 100%, 80.1%, and 70.0% for the adjuvant fractionated EBRT, SRS, and surveillance groups, respectively (p=0.026) (Supplementary Table 4, only online).

In contrast to the LC, the survival outcomes for patients with ACP and PCP were different. PFS and OS did not differ based on adjuvant treatment given to patients with PCP (Supplementary Figs. 4A and 5A, only online). The 5-year PFS rates in patients with PCP were 100%, 33.3%, and 67.3% in the adjuvant fractionated EBRT, SRS, and surveillance groups, respectively (p=0.205). The 5-year OS rates were 100%, 66.7%, and 81.3% in the adjuvant fractionated EBRT, SRS, and surveillance groups, respectively (p=0.848). However, survival outcomes were different in patients with ACP based on the adjuvant treatment received (Supplementary Figs. 4B and 5B, only online). The PFS was superior in the adjuvant fractionated EBRT than in the SRS and surveillance groups (5-year PFS; adjuvant fractionated EBRT vs. SRS, 100% vs. 64.7%, p=0.002; adjuvant fractionated EBRT vs. surveillance groups, 100% vs. 63.6%, p=0.003). The OS was superior in the adjuvant fractionated EBRT group than that in the SRS group (5-year OS: adjuvant fractionated EBRT vs. SRS, 100% vs. 82.4%, p=0.047; adjuvant fractionated EBRT vs. surveillance groups, 100% vs. 92.8%, p=0.245).

Toxicity

In the fractionated EBRT group, 20 and 13 patients had visual impairment at diagnosis (74.1%) and after operation (48.1%),

respectively (Table 3). After RT, more than 50% still had visual impairment. In the SRS group, 12 patients showed visual impairment at diagnosis (60.0%), and the visual impairment was decreased to five patients after surgery (25.0%). After SRS, 50% of patients showed visual impairment. In the surveillance group, more than 60% of patients had visual impairment at diagnosis,

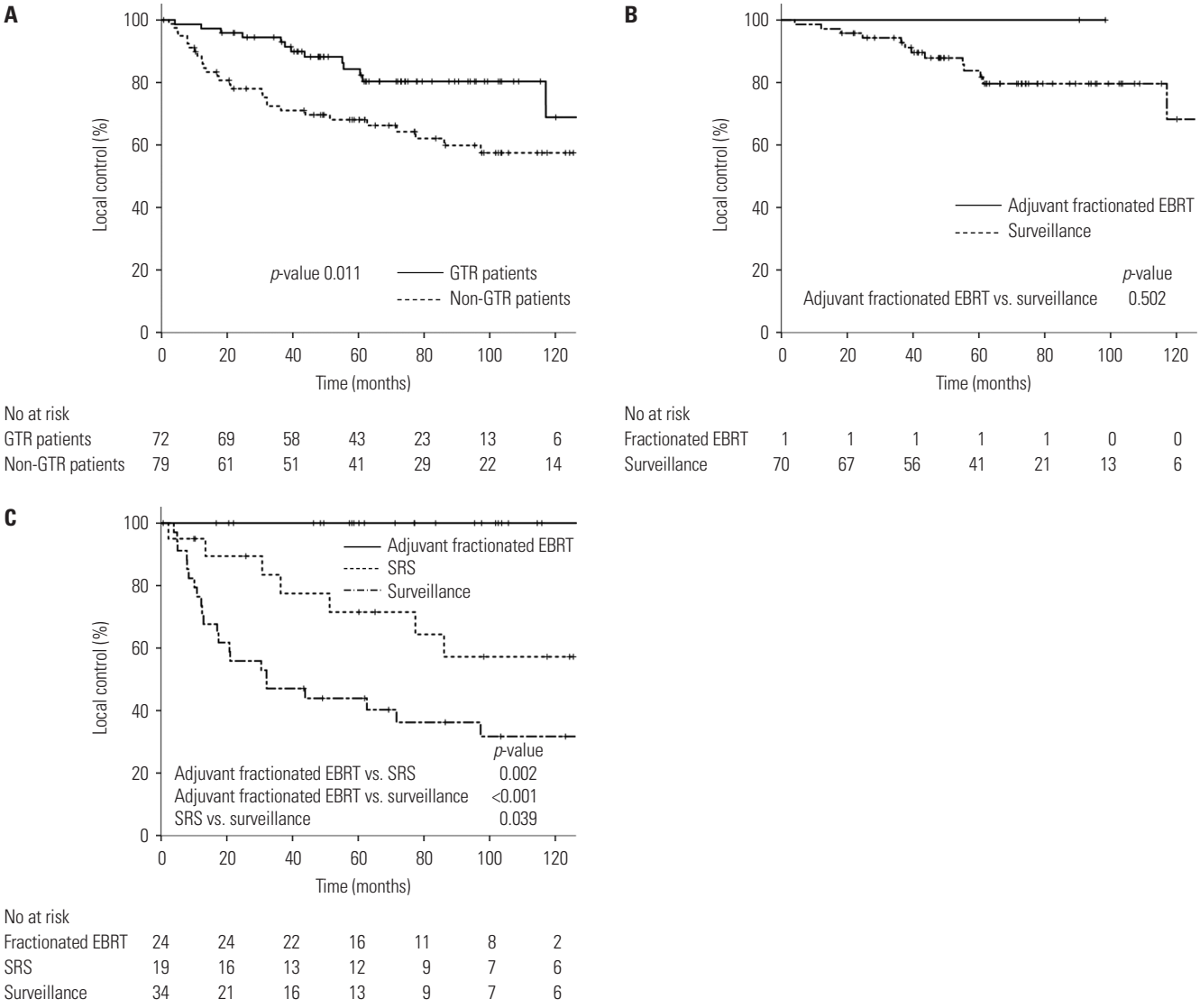

Fig. 2. Comparison of local control (A) in patients undergoing GTR and non-GTR, according to adjuvant treatment in (B) GTR patients and in (C) non-GTR patients. GTR, gross total resection; EBRT, external beam radiation therapy; SRS, stereotactic radiosurgery.

Table 3. Toxicity Profile of Patients

	Adjuvant fractionated EBRT (n=27)			SRS (n=20)			Surveillance (n=106)	
	Initial diagnosis	Post-surgery prior to RT	Post RT	Initial diagnosis	Post-surgery prior to RT	Post RT	Initial diagnosis	Post-surgery
Visual impairment								
G2	17 (63.0)	12 (44.4)	13 (48.1)	12 (60.0)	5 (25.0)	9 (45.0)	60 (56.6)	32 (30.2)
G3	3 (11.1)	1 (3.7)	1 (3.7)	0 (0)	0 (0)	1 (5.0)	12 (11.3)	4 (3.8)
Hormone deficiency								
Growth hormone deficiency	4 (14.8)	4 (14.8)	4 (14.8)	2 (10.0)	4 (20.0)	4 (20.0)	11 (10.4)	22 (20.8)
Diabetes insipidus	6 (22.2)	16 (59.3)	16 (59.3)	7 (35.0)	8 (40.0)	8 (40.0)	20 (18.9)	46 (43.4)
Panhypopituitarism	1 (3.7)	5 (18.5)	6 (22.2)	6 (30.0)	6 (30.0)	7 (35.0)	18 (17.0)	34 (32.1)

EBRT, external beam radiation therapy; SRS, stereotactic radiosurgery; RT, radiotherapy; G2, Grade 2; G3, Grade 3.
Data are presented as n (%).

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while 34% of patients showed visual impairment after treatment.

In the fractionated EBRT group, eight patients experienced improvement in visual impairment following treatment (29.6%), while two patients experienced a worsening of symptoms (7.4%). In the SRS group, four patients saw improvement (20.0%), whereas two patients experienced symptom aggravation (10.0%). In the surveillance group, 43 patients showed improvement (40.6%), but seven patients experienced a deterioration of symptoms (6.6%). The differences in symptom changes among the three groups were significant (p=0.031).

Hormone deficiency deteriorated after surgical resection. In all three groups, the number of patients experiencing hormone deficiency increased after surgery. In both fractionated EBRT and SRS groups, more than 90% of patients showed hormone deficiency regardless of RT after operation. None of the patients in any of the three groups experienced improvement in hormone deficiency after treatment. Hormone deficiency worsened in 15 patients in the fractionated EBRT group, four patients in the SRS group, and 53 patients in the surveillance group (fractionated EBRT vs. SRS vs. surveillance groups: 55.5% vs. 20.0% vs. 50.0%, p=0.029). Even though the EBRT group showed higher LC compared to SRS and surveillance groups, the EBRT group had higher rate of aggravation of visual impairment and hormone deficiency after treatment compared to other groups.

DISCUSSION

In this study, craniopharyngioma treated with adjuvant fractionated EBRT showed higher LC and PFS in non-GTR patients and acceptable treatment-related toxicity in the long term. Although the fractionated EBRT group had fewer cases of GTR and larger tumor sizes, it showed higher LC. In the multivariate analysis, the fractionated EBRT group remained significantly associated with higher LC. Regardless of tumor type, adjuvant fractionated EBRT was associated with higher LC.

In the 2021 WHO classification of CNS tumors, ACP and PCP are classified as distinct tumors. Several studies have shown that ACP and PCP differ in their clinical and histopathological characteristics.[16] We attempted to determine the optimal adjuvant treatment for distinct craniopharyngiomas based on this new classification. The management of craniopharyngioma includes surgery, irradiation, or a combination of both; however, this remains controversial and varies globally.[17-20]

The administration of adjuvant treatment for craniopharyngiomas has been debated for a long time.[21-24] Radical complete resection, as a primary treatment approach, is not always feasible for limiting toxicities to tolerable levels. A major challenge in achieving complete resection is the proximity of the tumor to anatomical structures, such as the hypothalamus or optic chiasms. Despite improved neurosurgical techniques, total macroscopic resection is still associated with poor treatment-related toxicity outcomes.[25,26] Our data demonstrated that adjuvant EBRT can result in excellent long-term tumor control while showing acceptable treatment-related toxicity. Previous reports have confirmed the efficacy of fractionated EBRT in craniopharyngioma, with a 10-year LC rate of 77%–89%.[8,9,27,28] Additionally, reduced toxicity has been reported after treatment with fractionated EBRT.[2,12] The superior LC with fractionated EBRT might be a result of the target volume, which includes the entire tumor bed, whereas the target volume for SRS only includes the residual tumor. Six marginal recurrence cases in SRS group showed 4 mm of mean distance between surgical cavity and failure sites. If fractionated EBRT had been performed, the failure site would likely have been within the target volume, potentially reducing the occurrence of marginal failure. However, fractionated EBRT increases the risk of hormone insufficiency; hence, SRS is used as an adjuvant treatment for craniopharyngioma, especially in younger patients.[10,29] Notably, hormone insufficiency commonly occurs before treatment due to the disease or after surgery, and less due to EBRT or SRS, in this study.

SRS has a high rate of recurrence in this study. It is challenging to perform fractionated EBRT as salvage treatment, and the risk of toxicity following re-operation is high.[3,30-32] Fractionated EBRT is an effective therapy for recurrent craniopharyngioma,[31,33,34] and our results demonstrated that none of the patients showed disease progression after treatment. The management of recurrent craniopharyngioma remains one of the most debated issues in neuro-oncology. When GTR can be achieved, it remains the treatment of choice. However, GTR is challenging to achieve in recurrent craniopharyngioma,[3,30,35,36] especially if RT has already been administered.[30] Given the difficulty in managing recurrent craniopharyngioma, the initial treatment should be approached with caution to prevent recurrence.

Several studies have confirmed that the clinical features of PCP and ACP are different.[16] To our knowledge, no studies have been conducted on treatment outcomes according to craniopharyngioma type. The LC of patients who received adjuvant fractionated EBRT was significantly superior in both the PCP and ACP groups compared to patients who received adjuvant SRS and those in the surveillance groups. None of the patients in the adjuvant fractionated EBRT group experienced local progression. Although ACP and PCP differ in their genesis and clinical features, adjuvant fractionated EBRT is an effective treatment for achieving LC of both ACP and PCP.

Although adjuvant fractionated EBRT showed higher PFS compared to other groups, one patient died in the adjuvant fractionated EBRT group. This patient succumbed to glioma, which occurred 94 months after RT. The glioma may have been caused by EBRT performed for the treatment of craniopharyngioma, especially when considering the location of the tumor. The glioma is located across the left cerebral peduncle, left basal ganglia, and left upper pons, and mostly overlaps with the radiation field. Furthermore, PFS did not differ according to adju-

vant treatment in the PCP group. This may be due to the smaller number of patients with PCP. The ratio of patients with PCP and ACP is approximately 1:3 epidemiologically, which is consistent with the findings in this study, resulting in a relatively smaller number of patients with PCP. Consequently, the PFS benefit of adjuvant fractionated EBRT in patients with PCP could not be demonstrated.

A high risk of damage is associated with the optic nerve after surgery or RT, as craniopharyngioma is adjacent to the optic pathway. Tumor compression of the optic chiasm also leads to visual impairment in patients with large tumors.[37] In several retrospective studies, radiation-induced optic neuropathy was rarely observed after adjuvant fractionated EBRT.[2,24,38] Radiation-induced optic neuropathy depends on the total dose and fraction size. In the Royal Marsden Hospital, among the 148 patients treated with surgery and RT with a median total dose of 50 Gy at a 1.5 Gy fractional dose, none developed optic neuropathy.[27] In other reports, none of the patients who received <2.5 Gy/fraction doses developed optic neuropathy.[39] Optic neuropathy would be very rare following a total dose of 54 Gy at 1.8 Gy/fraction, which was the dosing scheme used for the adjuvant fractionated EBRT group in our study. Although some patients experienced visual impairment after adjuvant fractionated EBRT, the contribution of adjuvant fractionated EBRT to visual impairment in these patients was likely minimal.

The pituitary gland is known to be sensitive to radiation, and hypothalamic-pituitary dysfunction can result from the high amount of radiation required to control craniopharyngiomas. The incidence of post-irradiation endocrinological dysfunction is difficult to interpret as most patients already present with endocrinological dysfunction due to surgical procedures. Diabetes insipidus is rarely caused by RT and is considered a complication of surgical management.[40] Significantly more patients (79%) were reported to develop diabetes insipidus in the surgery-only group compared to those in the irradiation group (22%). The incidence of panhypopituitarism was also higher in the surgery-only group.[8] This implies that hormonal deficiency is affected by RT; however, surgery appears to have a more significant effect on it. The toxicity caused by RT is mainly dependent on the dose.[41] Patients who received more than 60 Gy exhibited a higher rate of complications without an improvement in LC.[42] Since children are much more likely to suffer long-term toxicity from RT, it should be applied with caution. Therefore, while administering an adequate radiation dose for effective tumor control is important, it is also worth considering lower doses to reduce radiation-related toxicity, especially in children.

This study had several limitations. First, the patients were retrospectively identified in this study. Therefore, the selection of adjuvant treatments may be biased. Second, the analysis of treatment-related toxicity was limited. Finally, statistical significance could not be demonstrated due to the limited number of patients. However, despite these limitations, this study analyzed the treatment outcomes and toxicity according to adjuvant treatment for craniopharyngioma, depending on the craniopharyngioma tumor types.

In conclusion, adjuvant fractionated EBRT after surgery showed higher LC and PFS compared to SRS or surgery alone. Especially, in patients who underwent non-GTR, the adjuvant fractionated EBRT group showed better LC compared to the SRS and surveillance groups. The group that received adjuvant treatment tended to have residual tumors after tumor removal, and the fractionated EBRT group had larger tumor size. Despite limitations in the extent of resection and tumor size, the fractionated EBRT group demonstrated higher LC. Fractionated EBRT group was significantly associated with higher LC, even in multivariate analysis. Although treatment-related toxicities were not negligible, they remained tolerable. Clinicians should actively consider adjuvant fractionated EBRT for the treatment of craniopharyngiomas in patients who did not undergo GTR. Further studies are necessary to draw robust conclusions regarding the causal relationship between each treatment and toxicity.

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