Master's Thesis of Translational Medicine

Comparative Analysis of Surgical Outcome and Safety of Transcranial Approach and Transsphenoidal Approach, Focusing on Anatomical Classification in Pediatric Craniopharyngioma

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Abstract

Objective: We aim to compare transsphenoidal approach (TSA) and transcranial approach (TCA) in pediatric patients with craniopharyngioma (CRP). Oncological and neruendocrinological outcomes of 3 types of different anatomic tumor subclassifications are compared to find possible indications for TSA or TCA. The prognostic factors for recurrence are also re-evaluated.

Methods: A retrospective review was conducted on patients under 20 years of age who underwent surgical treatment for pathologically proven craniopharyngioma between July 1998 and December 2019. The patients were divided into TSA and TCA groups. CRPs were divided into anatomic subtypes using tumor relationship with the diaphragm, the infundibulum and the arachnoid membrane. Data on oncological and neuroendocrinological outcomes were collected. Kaplan-Meier curves were used to estimate progression-free survival, and Cox regression was employed to elucidate risk factors for recurrence.

Results: A total of 112 patients were included in this study, with 75 patients in the TCA group and 37 patients in the TSA group. The overall 5-year PFS was 64 ± 5 % for the entire cohort. The extent of resection (P = 0.116), progression-free survival (P = 0.566) and recurrence rates (P = 0.498) were comparable between the two groups. The oncological and neuroendocrinological results across TSA and TCA groups in each tumor subtypes were also comparable. TSA displayed superior ophthalmological outcomes in preinfundibular type CRPs (P = 0.027). The extent of resection (HR 0.12, 95% CI 0.05-0.29, P < 0.001) and subdiaphragmatic tumor components (P = 0.017) were the most significant risk factors for recurrence in univariate and multivariate analyses.

Conclusions: Regardless of anatomic tumor subtypes defined by tumor relationship to the chiasm, diaphragm, infundibulum and the arachnoid membrane, TSA is a safe and effective alternative to TCA in pediatric CRP resection. Our study results indicate that TSA

results in superior ophthalmological outcomes in the subdiaphragmatic type of CRPs. The extent of resection and the presence of subdiaphragmatic tumor components were the most significant risk factors for recurrence in pediatric CRPs.

Keyword : Craniopharyngioma, Pediatric, Transsphenoidal, Transcranial, Approach
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Chapter 1. Introduction

Craniopharyngiomas (CRPs) are thought to arise from the remnants of Rathke's pouch, and comprise of 2 to 5 % of all central nervous system tumors [1, 2]. With bimodal age distribution, approximately one third to half of CRPs occur in children between ages 5 to 14 years [3, 4]. Although histologically benign, CRPs pose a considerable challenge to neurosurgeons due to their central location and proximity to vital neurovascular structures [5, 6].

Some studies have reported that subtotal resection (STR) and adjuvant radiation therapy achieved similar rates of disease control to gross total resection (GTR) and yielded better neuroendocrinological outcome [7-9]. However, the extent of resection is still the most important predictor of recurrence [10]. Recurrence after gross total resection is dependent on the anatomic location of CRPs, as those with intrasellar components tend to recur more frequently [5]. To achieve GTR with minimal neurologic damage, meticulous surgical planning guided by the anatomic location of the CRPs is crucial [6, 11]. Different types of CRP classifications have been proposed to predict surgical outcome and to aid the selection of optimal surgical approach [6, 11, 12]. We previously have reported the choice of surgical methods based on the tumor

relationship with the optic chiasm and the diaphragm sellae [12]. According to this indication, we have performed transsphenoidal approach (TSA) in subdiaphragmatic tumors with competent diaphragm sellae and have reported favorable clinical outcomes [13]. Since then, there has been new tumor classification suggestions based on the tumor relationship with the infundibulum [6], and another scheme based on the presence of an arachnoid envelope around the tumor [11]. Fan et al also have suggested that TSA can achieve greater GTR rates in prechiasmatic, subdiaphragmatic tumors, and the results are in line with our previous study [11, 12].

Whilst the choice between TSA and transcranial approaches (TCAs) still remains a matter of debate, some reports have indicated that TSA is superior to TCA in certain tumor types, especially in subdiaphragmatic and prechiasmatic tumours [11, 12, 14]. Also, recent advances of endoscopic endonasal skull base surgery (EES) has provided a unique advantage of direct and wide surgical view [1]. With the development of endoscope optics, neuronavigation and microinstrumentation, indications for TSA have been extended to include retrochiasmatic tumors as well [6, 15].

Our data comprise of 20 years of follow-up in CRP patients treated with both TCA and TSA. In this report, we aim to update predictors for long-term recurrence after gross total resection. We also aim to

validate the feasibility of TSA in children, and its indication according to different tumor classifications. We classified CRPs according to their relationship with the diaphragm sellae, the infundibulum, and the arachnoid membrane to examine the surgical outcomes of TCA and TSA by tumor types [6, 11, 12, 15]. By analyzing the neuroendocrinological outcomes, we seek to identify the optimal surgical strategy for each tumor types [6, 11, 12].

Patients and Methods

A retrospective analysis was performed on patients under 20 years of age who underwent the operation for pathologically proved CRPs from 1998 to 2019. The patient's medical records and magnetic resonance images (MR) were reviewed for data collection. We excluded patients without available preoperative or follow-up MR images regardless of the reasons (Figure 1). All primary cases of CRPs were included in our study. Also, as our institution is a tertiary center that receives referrals from local hospitals, patients with history of prior CRP resection who underwent surgery for recurrence were included in this study. Such referrals included residual tumors after incomplete excision. A pathologist reviewed the craniopharyngioma subtypes as papillary or adamantinomatous. This study was approved by the Institutional Review Board of Seoul National University Hospital (IRB no. H-2104-154-121) and the informed consent was waived for the retrospective nature of the study.

T1 weighted MR images with gadolinium contrast and T2 weighted MR images were used to assess the preoperative anatomical features and evaluate the postoperative extent of tumor removal. To analyze the tumor characteristics, the location of the tumor was categorized

by its relationship with the diaphragm sellae [16], the pituitary stalk [6], or the arachnoid membrane [17]. The degree of hypothalamic damage was evaluated according to Puget's classification, which ranges from grade 0 to 2 - grade 0 indicates no hypothalamic damage, grade 1 denotes hypothalamic displacement by tumor, and grade 2 designated in cases with severe hypothalamic damage [18]. The presence of obesity (body mass index [BMI] >25), which reflect the severity of hypothalamic damage, were also recorded [19]. Hydrocephalus was diagnosed when ventriculomegaly (Evans' index ≥ 0.3) was combined with periventricular white matter changes seen on T2 weighted MR images [20].

We measured the pre- and post-operative tumor volume with the volumetric method on MR T1 weighted image with contrast enhancement using INFINITT PACS® (2002-2020 INFINITT Healthcare Co., Ltd. Seoul, Korea) to evaluate the extent of tumor resection. Postoperative MR images with gadolinium enhancement were obtained within 48 hours after surgery. Extent of resection was divided into two groups, GTR and STR. GTR was defined as no intraoperative residual tumor and no residual tumors on postoperative MR (100% resection). STR was defined as records of intraoperative residual tumor capsules or adhesions, and/or residual mass detected by the postoperative MR (<100% resection). Surgical

records and intraoperative photographs were assessed for thin residual capsules that may not be visible on postoperative MR.

Tumors were grouped using anatomical classifications as defined by Wang et al., [16] Kassam et al., [6] and Liu et al. [17]. Wang et al. [16] described tumor classification by its relation to the diaphragm. Subdiaphragmatic tumors with intact diaphragm sellae are located in the sella underneath intact diaphragm, and often displace the optic chiasm upward as the tumors grow. Purely supradiaphragmatic CRPs with intact diaphragm do not involve the pituitary gland, which is enveloped by the diaphragm sella. The pituitary stalk is typically intermingled with the tumor, however. Subdiaphragmatic CRPs without intact diaphragm often show a snowman appearance as they have subdiaphragmatic component as well as supradiaphragmatic extensions (Figure 2). Kassam et al. [6] classified CRPs using its location relative to the infundibulum. Preinfundibular tumors lie anterior to the infundibulum and the pituitary stalk, and the optic chiasm is characteristically elevated by the tumor. Transinfundibular CRPs widen and obliterate the pituitary stalk and extend towards the anterior third ventricle. Retroinfundibular tumors are located in the retroinfundibular space, and may propagate rostrally towards the anterior third ventricle (type IIIa) or caudally into the interpeduncular fossa (IIIb) (Figure 3). Lastly, Liu et al. [17] have

proposed a CRP classification system based on the main tumor location. Type Q tumors (Q-CRPs), like the subdiaphragmatic tumors defined by Wang et al., arise beneath the diaphragm and the pituitary gland is involved. The shape of tumors bulging upward and stretching the diaphragm appear like a letter "Q" and they are named thus. Type S CRPs (S-CRPs) usually arise from the middle to lower third portion of the pituitary stalk, and the shape of pituitary stalk distorted by the tumor seems like a letter "S." Type T tumors (T-CRPs) originate from the tubero-infundibulum, have subarachnoid location, and typically occupy the third ventricle (Figure 4). The patient populations were then subdivided by anatomic tumor classification and the type of surgical approach to analyze oncological and neuroendocrinological outcomes. This was done to identify possible indications for TCA and TSA according to different anatomic CRP subtypes.

Surgical approaches were divided into TCA including interhemispheric subfrontal (N = 62), anterior transcallosal (N = 4), and pterional (N = 9) approaches, or TSA comprising of microscopic TSA (N = 5) and endoscopic endonasal approaches (ESS, N = 32). Image-guided neuronavigation was employed in all cases of TCA and TSA since 2007. Prior to 2010, microscopic TSA was employed in select cases in our hospital [13]. ESS was introduced in 2010 at our

institution and the surgeries were performed via transplanum/tuberculum, or transsellar routes with neuronavigation [15]. The surgical approaches were determined by the size and the location of the tumor in relation to adjacent neurovascular structures. TCA had priority in cases with frontal extension of tumor with cortical cuff, tumors extending lateral to the interal carotid artery (ICA) bifurcations in the coronal plane, or purely intraventricular tumors. Also, TCA was primarily employed in children under the age of 5. The presence of tumor in the posterior fossa was not a limiting factor in opting for TSA. However, TSA was not recommended in patients under the age of 5 due to the narrow nasal corridor and difficulties with postoperative nasal care. The pituitary stalk was sacrificed if tumor invasion was noted. In TSA cases, the skull base was reconstructed with a vascularized nasoseptal flap. Since 2019, we have employed a new skull base reconstruction method using multi-layer onlay graft utilizing hydroxyapatite cement [21]. For extended TSA cases with high-flow cerebrospinal fluid (CSF) leakage, we reconstructed the skull base with fibrin sealant patch (FSP), hydroxyapatite cement, and pedicled nasoseptal flap without CSF diversion.

We attempted radical excision in every case and when this was not feasible, adjuvant therapy including radiation therapy or gamma knife

radiosurgery were employed at the discretion of our multidisciplinary team. The postoperative adjuvant therapy for remnant tumor was performed 3 months after surgical excision, and the choice of adjuvant therapy modality was based on the tumor characteristics including the size and shape, presence of cystic portions, and the distance to the optic apparatus. Radiation doses administered ranged between 50.4 Gy to 54 Gy, and gamma knife doses ranged from 7.5 Gy to 20 Gy, with most patients receiving 15 Gy.

Follow-up MR images were obtained biannually for the first 2 years after surgery, and yearly follow-up was conducted for the next 3 years. After 5 years of follow-up, MR images were scheduled in every two years.

Ophthalmological evaluation included the best corrected visual acuity and objective visual field examination by Goldmann or Humphrey perimetry before and 6 months after surgery. Visual state was re-assessed when recurrence was noted on follow-up MR images. Deterioration of vision after adjuvant therapy was also recorded. Patients too young to undergo Goldmann or Humphrey perimetry were evaluated using confrontation test.

Hypothalamic symptoms such as cognitive and/or behavioral dysfunction and obesity were identified. Patients with neuropsychiatric test results displaying cognitive dysfunction or

qualitative descriptions of cognitive and/or behavioral problems in medical records were noted. Patients with records of neuropsychiatric test results with intelligent quotient (IQ) below the average and documentation of kleptomania, hypothalamic hyperphagia, emotional dysregulation, and episodes of acting out were identified as having both cognitive and behavioral dysfunctions.

Functional status of patients were assessed pre- and postoperatively using the Karnofsky performance status scale (KPS) and modified Rankin scale (mRS). The KPS classifies patients from 0 to 100 with intervals of 10, with 0 indicating death and 100 indicating no evidence of disease [22]. The lower the KPS, the worse the functional status of a patient. mRS ranges from 0 to 6, with 0 being asymptomatic and 6 representing death [23].

Preoperative basal endocrinologic evaluation measured levels of thyroid-stimulating hormone, total T4, free T4, adrenocorticotropic hormone (ACTH), cortisol, growth hormone, insulin-like growth factor-1, prolactin, luteinizing hormone, follicle-stimulating hormone, estradiol and testosterone from serum sampled in the early morning before 8 am. Combined pituitary function tests were not performed preoperatively. However, rapid ACTH stimulation test was adopted in cases with hypocotosolism symptoms or low cortisol level on basal hormone studies. In cases with hypopituitarism and

diabetes insipidus, operation was performed after adequate hormone replacement have been administered. The postoperative endocrinological evaluation assessed the same items as preoperative evaluations, and was conducted at 1 month and 3 months after surgery, and then at every 6 months. In cases with pituitary stalk preservation, insulin tolerance test was performed at postoperative 3 months. The endocrinological outcomes were re-assessed after identification of the tumor recurrence, and deterioration was defined as impairment in any one of the pituitary axes.

Statistical analyses were performed using IBM® SPSS® Statistics 25.0 (© 2017 IBM Corp. NY, USA). The Chi-square or Fisher's exact tests were employed to compare categorical variables, and T-tests and ANOVA were used to evaluate continuous variables. Survival analysis with Kaplan-Meier curves were performed to plot the progression-free survival (PFS), and log-rank tests were used to compare PFS between TSA and TCA groups. Cox regression model was used to delineate statistically significant prognostic factors in univariate and multivariate analyses. Results were considered significant if $p \leq 0.05$, and p-values were 2-sided.

Results

Patient population (Table 1)

A total of 112 patients were included, consisting of 65 boys and 47 girls. The sex ratio were 44:31 and 21:16 in the TCA and TSA groups, respectively. The mean age at treatment for the cohort was 7.6±3.8 years. There was a statistically significant difference in mean age between the TCA and the TSA groups, with a lower mean age (6.5 ± 3.5 years) in the TCA group and a higher mean age (10.0 ± 3.3 years) in the TSA group (P<0.001).

The functional status also differed between the two groups, as a better functional status in the TSA group is indicated by a higher mean KPS (65.6 ± 11.7 vs 72.7 ± 13.7, P = 0.005) and lower mean mRS (3.0 ± 0.8 vs. 2.4 ± 1.0, P = 0.004) scores. This was reflected by the greater mean Puget grade in the TCA group indicating greater degree of hypothalamic damage (1.65 ± 0.53 vs. 1.27 ± 0.77, P = 0.009). Resultantly, the percentage of patients with preoperative Puget grade 2 reflecting severe hypothalamic damage was greater in the TCA group (68% vs. 45.9%, P = 0.006).

On the other hand, baseline visual impairment did not differ between the two groups. The number of patients who complained of visual field defects or decreased visual acuity were 49 (71.0%) and

25 (67.6%) in the TCA and the TSA groups, respectively. There were greater number of patients with preoperative obstructive hydrocephalus in the TCA group compared to the TSA group, but the difference was not statistically significant (52.0% vs. 35.1%).

Larger percentages of patients in the TSA group presented with hormonal abnormalities. Hypothyroidism, hyposomatotropism, and hypogonadism were more prevalent in the TSA group (P = 0.042, 0.019 and 0.025, respectively). Presence of diabetes insipidus, however, were similar across the two groups.

In total, 23 patients had received prior surgical resections via either TCA or TSA, or CSF diversions including ommaya reservoir insertion, ventriculoperitoneal shunt, or external ventricular drainage at other institutions prior to tumor resection at our hospital. 8.0% of TCA patients and 16.2% of TSA patients had received TCA. 1.3% of TCA groups and 2.7% of TSA groups had underwent TSA previously. Two patients in the TCA group and 5 patients in the TSA group were treated with cyst fenestration prior to primary tumor resection. One patient in each group had emergency external ventricular drainage placement before being transferred to our institution.

Tumor characteristics (Table 2)

The study group comprised of 95 patients (84.8%) with primary

CRPs and 17 patients (15.2%) with recurrent CRPs. The percentage of recurred tumors were greater in the TSA group (9.3% vs. 27.0%, P = 0.014). Maximal tumor diameter were significantly different in the two groups, with larger tumors in the TCA group (4.29 ± 1.07 vs. 3.43 ± 1.35, P < 0.001). Nonetheless, volumetric analysis calculated as the sum of area of axial slices on MR images did not show statistically significant difference between the TCA and the TSA groups (26.1 ± 40.9 12.9 ± 10.8).

Three anatomic classification schemes for CRPs were used [16] [6]. Overall, fourty-three cases (38.4%) were subdiaphragmatic with intact diaphragm, 53 cases (47.3%) were supradiaphragmatic tumors, and 16 cases (14.3%) were subdiaphragmatic CRPs with incompetent diaphragm according to tumor location relative to the diaphragm [16]. The distribution of CRPs in relation to the chiasm did not differ between the TCA and TSA groups. Tumor classification relative to the infundibulum by Kassam et al., however, did show a significant difference in distribution between the TCA and the TSA groups (P < 0.001) [6]. Lesser number of preinfundibular CRPs were treated by TCA rather than (4.0% vs. 32.4%, P < 0.001) whereas most of retrochiasmatic tumors were resected by TCA (77.0% vs. 37.8%, P < 0.001). Tumor grouping by another classification system proposed by Liu et al. utilizing main tumor location, did not differ

across the two groups (P = 0.292).

Comparison of surgical outcomes between groups divided by anatomic CRP classifications and the type of surgical approach (Table 3)

The patient populations were subdivided by anatomic tumor classification and the type of surgical approach to help determine the most appropriate surgical approach for each tumor classification schemes. The extent of resection were comparable between the TCA and TSA groups in subdiaphragmatic CRPs with intact diaphragm, supradiaphragmatic CRPs and subdiaphragmatic tumors with incompetent diaphragm. This trend was similar throughout other anatomic classification schemes. Thus the choice of surgical approach did not affect the extent of resection in different tumor anatomic subtypes. Similarly, adjuvant therapy were utilized at a similar rate across tumor subtypes. Greater number of patients in the TSA group with preinfundibular tumors experienced improved visual outcome (P = 0.027). In supradiaphragmatic CRPs, transinfundibular CRPs, retroinfundibular CRPs, S-CRPs and T-CRPs, infection rates were significantly higher in the TSA groups (P < 0.001, 0.023, < 0.001, 0.047, and 0.001, respectively).

Kaplan-Meier curves comparing PFS rates between groups

defined by tumor relationship with the diaphragm [16] is shown in figure 5. Interestingly, subdiaphragmatic tumors with incompetent diaphragm, indicating both the presence of subdiaphragmatic component and retrochiasmatic growth into the hypothalamus and third ventricle, had the best PFS. The differences between PFS according to tumor subtypes were not statistically different. Likewise, tumor classification relative to the infundibulum [6] displayed similar PFS across groups (Figure 6). On the other hand, classification by Liu et al.[17], did show a significantly better PFS in S-CRPs compared to the other two tumor subtypes, namely Q-CRPs and T-CRPs (P = 0.027) (Figure 7).

Oncological outcome (Table 4)

The mean duration of follow-up in months was 113.5 ± 73.6 for the entire patient population, and was significantly longer in the TCA groups (127.1 ± 75.1 vs. 85.95 ± 62.8, P = 0.003). Overall 5-year PFS was 64 ± 5 % for the entire cohort (Figure 8A). The mean time to progression was 22.7 +- 16 months and the median time to progression was 31 months.

The extent of resection did not significantly differ between the TCA and the TSA groups, although the TSA groups did show a slightly higher GTR rate (86.5% vs. 73.3%). GTR groups had a

significantly longer PFS as seen in figure 8B (Log-rank test $P < 0.001$). To examine whether STR with adjuvant therapy had a better PFS, the PFS of GTR group (100% resection), the STR group (<100% resection), and the STR group with adjuvant therapy were compared. The STR group with adjuvant therapy showed a slightly better PFS than the STR group, but the PFS were significantly worse compared with that of the GTR group ($P < 0.001$) (Figure 8C). The maximal diameter of residual tumors were similar between the two groups (0.27 ± 0.62 vs. 0.14 ± 0.34). Residual tumor volume estimated by sum of areas on axial postoperative MR images, however, were significantly higher in the TCA group (0.4 ± 1.5 vs. 0.04 ± 0.09, $P = 0.020$). Pathologic examinations revealed all tumors to be adamantinomatous type CRPs, and there were no papillary CRPs in our cohort.

Complications of surgical resection of CRP for the entire cohort included mortality (2 cases, 1.8%), hemorrhage or infarction (13 cases), infection (14 cases), CSF leakage (2 cases) and seizure (9 cases). Mortality was observed only in the TCA group, although there was no statistical difference between the TCA and the TSA group. Hemorrhage or infarction rates were similar across the two groups. Infection, however, was more prevalent in the TSA group (TSA vs. TCA: 32.4% vs. 2.7%, $P < 0.001$). Figure 9 displays annual

percentages of each surgical approach (Figure 9A) and infection rates (Figure 9B) in the TCA and TSA groups. It can be observed that the TSA infection rates peaks in 2007 then gradually decreases towards 2019. Lastly, seizure were observed only in the TCA group (12.0%, P = 0.029).

Adjuvant therapy for subtotal resection included 11 cases of radiation therapy and 12 cases of gamma knife radiosurgery. The mean time from surgical resection to adjuvant therapy was 29.19 ± 32.07 in the TCA group and 19.57 ± 16.28 months in the TSA group. The distribution of adjuvant therapy modalities among the TCA and TSA groups were comparable. Recurrence rates were also similar across the groups (33.3% vs. 28.6%). Mean time to recurrence in months was 19.92 ± 14.73 in the TCA group and 29.60 ± 17.63 in the TSA group. The most common site of recurrence was the sella (20 cases, 17.9%), followed by the optic chiasm (5 cases), hypothalamus (4 cases), the third ventricle (2 cases) and the pituitary stalk (1 case). Other sites of recurrences include frontal base, cerebellopontine angle and temporal base (4 cases). There was no statistically significant difference in the location of recurrence between the TCA and TSA groups.

Factors for recurrence (Table 5)

Univariate and multivariate Cox regression were used to define factors for CRP recurrence. Extent of resection, type of surgical approach, aforementioned 3 anatomic tumor classification systems according to tumor relation to chiasm [16], infundibulum [6] and tumor location[17], tumor volume and size, and presence of previous recurrences were identified as possible contributors to recurrence. In univariate analysis, extent of resection was the most significant factor (HR for GTR 0.20, 95% CI 0.10−0.40, $P < 0.001$), followed by anatomic classification suggested by main tumor location [17] (HR = 1 for Q−CRPs and 0.25 for T−CRPs, $P = 0.048$). The three factors were also statistically valid in multivariate analysis. Surgical approach, tumor volume, size or previous recurrence did not play a significant role in predicting CRP recurrence. GTR groups displayed a significantly superior PFS compared to the STR group (Log−rank test $P < 0.001$, Figure 8A). The type of surgical approach did not impact the CRP recurrence (Figure 8D).

The groups were then split into GTR and STR subgroups and the PFS between primary and recurrent tumors were compared. Although the log−rank P−value was not statistically significant, recurrent CRPs with GTR were more likely to have shorter PFS than primary CRPs with GTR (Figure 10A). In STR group, the presence

of previous recurrence did not impact the PFS (Figure 10B). Conversely, in primary CRPs, the extent of resection was a significant predictor of PFS (Log-rank test $P < 0.001$, Figure 11A). Extent of resection was not a prognostic factor for recurrence in recurrent tumor group (Figure 11B).

Neuroendocrinological outcome (Table 6)

Postoperative functional outcome assessed by KPS and MRS were similar between the two groups (78.3 ± 18.0 vs. 80.5 ± 19.9 and 1.9 ± 1.3 vs. 1.7 ± 1.4 respectively). The extent of hypothalamic damage as denoted by the Puget grade, however, did show a significantly better results in the TSA group (TSA vs. TCA: 1.3 ± 0.8 vs. 1.7 ± 0.5, $P = 0.005$). The occurrence of symptomatic hypothalamic dysfunction, however, were comparable between the two groups (16.0% vs 21.6%). Overall, there were 9 cases with documented cognitive impairment, 4 cases with behavioral dysfunction, and 7 cases with both cognitive and behavioral dysfunction. Obesity, reflecting the degree of hypothalamic injury, were found in 36 patients. The obesity rates were 36% and 32.4% in the TCA and TSA groups, respectively. Mean BMI was 23.1 ± 5.7 in the TCA group, and 23.1 ± 5.4 in the TSA group.

35 patients (31.3%) experienced improved vision after surgical

resection of CRP, whereas 27 patients (24.1%) remained stationary and 28 patients (25%) complained of visual deterioration. The percentage of patients with postoperative visual improvement was slightly greater in the TSA group (TSA vs. TCA: 35.1% vs. 29.3%) but this was not statistically significant. On the other hand, a significantly greater proportion of patients experienced pituitary function deterioration in the TCA group (84.0% vs. 64.9%, P = 0.026), indicating better endocrinological outcome in the TSA group. None of the patients in the entire cohort experienced hormonal improvement after surgery for CRP. The prevalence of panhypopituitarism did not differ between the two groups (96.0% vs. 86.5%). Greater number of patients in the TCA group experienced diabetes insipidus (97.3% vs. 78.4%, P = 0.002).

Discussion

Demographic characteristics including age, functional status, the degree of hypothalamic involvement, and baseline pituitary function were disparate between the TCA and TSA groups. The difference in mean age of patients between the two groups reflect our policy in performing TSA above the age of 5. TSA is difficult to be employed in patients younger than the age of 5 due to the width of the pyriform apertures, narrower nasal cavity, and potential hindering of nasal and midface growth [1].

Patients in the TSA group presented more frequently with hypothyroidism, hyposomatotropism, and hypogonadism. The greater incidence of pituitary derangements in the TSA group may reflect glandular involvement with tumor in this group.

Over 20 years, our surgical paradigm have changed from mostly employing TSA in subdiaphragmatic type tumors to extending its utilization in supradiaphragmatic type tumors. Until 2010, when EEA was introduced in our institution, patients with larger supradiaphragmatic tumors were more likely to undergo TCA for tumor resection. Microscopic TSA were available and were applied in select cases of subdiaphragmatic tumors with intact diaphragm prior to 2010. Thus, this difference is echoed in the greater degree

of hypothalamic involvement in the TCA group. The mean Puget grade [18] was greater in the TCA group and the percentage of Puget grade 2 indicating severe hypothalamic damage was also greater in the TCA group. Preinfundibular tumors, which are unlikely to have hypothalamic extension as defined by Kassam et al. [6], were also typically treated by TSA than TCA.

Interestingly, greater percentage of tumors in the TSA group were recurrent. This coincides with our result showing the most frequent tumor recurrence site as the sella. Sellar recurrences comprise of 17.9% of the overall patients, 16.0% of the TCA cohort and 21.6% of the TSA group. TSA provides a direct surgical corridor that avoids damaging the basal cistern perforating arteries, and are more useful in recurrences that are limited to the sellar floor. The sellar floor and the underside of the optic chiasm is difficult to visualize via TCA surgical view, and this could be a possible explanation for the greater frequency of residual tumors occurring in the sella and optic chiasm.

We defined GTR was defined as no intraoperative residual tumor and no residual tumors on postoperative MR (100% resection) and STR as less than 100% of resection. We combined near total resection (NTR) with STR group as we found that STR and NTR has similar rates of recurrence. Even small residual tumor capsule invisible on postoperative MR images can lead to recurrences. Our

institution’s goal of surgical resection is GTR whenever possible, and our results showed the extent of resection was the most significant factor for predicting recurrence. TSA was superior in removing greater extent of tumor, as indicated by a significantly smaller residual volume compared to that in the TCA group.

The endocrinological outcomes were superior in the TSA group. Greater percentage of patients exhibited worsened endocrinological outcome in the TCA group and lesser number of patients were afflicted with diabetes insipidus in the TSA group. Also, in preinfundibular type proposed by Kassam et al. [6], statistically significant number of patients experienced visual improvement in the TSA group. This is attributable to less brain retraction and wider endoscopic view provided by TSA. Without the need for optic chiasm retraction, surgeons utilizing TSA can proceed safer tumor resection with lesser risk of optic chiasm injury [11, 15].

However, TSA patients experienced significantly greater postoperative infections in contrast to the TCA patients. Recently, we have begun to employ a watertight multi-layer onlay skull base reconstruction technique in patients undergoing extended TSA to reduce CSF leakage rates [21]. The new reconstruction technique consists of covering the bony defect in the sellar floor with fibrin sealant patches, then covering the entire fibrin sealant patch and

surrounding skull base with hydroxyapatite cement. After the cement is consolidated, pedicled nasoseptal flap is positioned onto the cement and held in place with oxidized cellulose and hydrogel sealants. The infection risks in adult group have fallen dramatically with the use of aforementioned reconstruction method [21], and this may improve infection rates in pediatric population as well. Similarly, our pediatric TSA infection rates peaked in 2007 and have fallen steadily over the years. There was no cases with postoperative infection in 2018 and 2019. Further studies in pediatric population are needed to demonstrate the effectiveness of new skull base reconstruction method.

The choice of surgical method did not alter recurrence rates or PFS, indicating that TSA is a viable alternative in children with CRPs. We have speculated that recurrent CRPs will have greater tendency to recur, and recurrence would be less likely to be determined by the extent of resection compared with primary tumors as stated in our previous study [15]. The results of our current investigation reiterated our hypothesis, as PFS were significantly better in primary tumors with GTR compared with primary tumors with STR, but PFS did not have significant difference between recurrent tumors with GTR versus recurrent tumors with STR. This reflects that recurrent tumors are more likely to recur despite gross total resection.

Although the log-rank test P-value was not statistically significant, there was a clear trend for better PFS in the primary CRPs with GTR compared to recurrent CRPs with GTR. This trend was also observed in a study by Dho et al., who showed that the extent of tumor resection and visual improvement are dependent on whether the tumor was primary [15]. There has been a trend in the literature reiterating that STR with RT is superior to GTR, as the STR group experienced less morbidity and RT achieved PFS similar to that of GTR [7-9]. Attempt at GTR via TCA frequently resulted in severe neurologic deficit or hypothalamic damage due to excessive retraction of the optic chiasm or the brain parenchyme, and led the current literature to favor STR with RT [24]. However, with the advance of TSA techniques and equipment, and thus the greater feasibility of achieving GTR via TSA with minimal neurologic deficit, GTR is again becoming the goal of surgery and gradually regaining the spotlight [15]. Unlike the reports asserting that subtotal resection with adjuvant therapy yields PFS comparable to that of GTR [7-9], our data showed contrary results. The PFS of the STR and STR with adjuvant therapy groups were similar, far inferior to that achieved by the GTR group.

The anatomical locations and growth patterns of CRPs are considered crucial in determining a surgical plan. We have used three

different anatomic schemes clarifying tumor types in relation to the optic chiasm, the infundibulum, and the diaphragm [6, 16, 17]. CRP classification with tumor location relative to the chiasm and the integrity of the diaphragm has been proposed by Wang et al. [16]. Previously, our group have proposed that the site of CRP origin relative to the diaphragm dictates tumor growth patterns [12]. As subdiaphragmatic tumors with intact diaphragm are separated from critical neurovascular structures by outstretched diaphragm, they are more easily dissected. Also, as subdiaphragmatic CRPs with intact diaphragm often displace the optic chiasm upward, TCA further places strain on the chiasm by brain retraction. Therefore, TSA was suggested to be more suitable for subdiaphragmatic type tumors with intact diaphragm [12]. However, in the present study, we were able to demonstrate that TSA outcomes of CRP resections are comparable to TCA in all tumor subtypes. When Kaplan–Meier curves for PFS is plotted for classification by Liu et al. [17], a significantly better PFS in S–CRPs compared to other two tumor subtypes were observed. This may implicate that Q–CRPs have subdiaphragmatic components, where most recurrences occur, and T–CRPs have subarachnoid locations and tight adhesions with the brain parenchyma, thus making it difficult to perform GTR.

Overall, the factors for recurrence that proved to be significant

were the extent of resection and the presence of subdiaphragmatic tumor. This was in line with our previous report on adult craniopharyngiomas [2]. Univariate and multivariate analysis revealed the extent of resection as the most significant factor predictive of PFS. The gross total resection rate of TSA did not differ with that of TCA in all anatomical tumor subtypes. If postoperative infection rates could be improved with the newly adopted skull base reconstruction method [21], TSA could be a safe and effective alternative to TCA in pediatric CRP patients.

Conclusions

Regardless of anatomic tumor subtypes defined by tumor relationship to the diaphragm, infundibulum and the arachnoid membrane, TSA is a safe and effective alternative to TCA in pediatric CRP resection. Our study results indicate that the employment of TSA does not have to be limited by retrochiasmatic or retroinfundibular tumor locations. The presence of prior recurrence may play a role in predicting future recurrence.

Table 1. Preoperative clinical features of patients

Total (N = 112)	**TCA (N = 75)**	**TSA (N = 37)**	**P-value**
Sex (M:F)	44:31	21:16	0.847
Age (years), Mean± SD	6.5±3.5	10.0±3.3	<0.001
Functional status, Mean ± SD			
Karnofsky performance status scale	65.6 ± 11.7	72.7 ± 13.7	0.005
Modified Rankin scale	3.0 ± 0.8	2.4 ± 1.0	0.004
Hypothalamic involvement [18]			
Mean Puget grade	1.65 ± 0.53	1.27 ± 0.77	0.009
Puget grade 0	2 (2.7)	7 (18.9)	0.006
Puget grade 1	22 (29.3)	13 (35.1)	
Puget grade 2	51 (68.0)	17 (45.9)	
Ophthalmologic status, n (%)			
Visual impairment (N = 106)	49 (71.0) * 6 missing cases	25 (67.6)	0.713
Hydrocephalus, n (%)			
Normal ventricle size	36 (48.0)	24 (64.9)	0.063
Presence of hydrocephalus	39 (52.0)	13 (35.1)	
Endocrinologic status, n (%)			
Hypothyroidism (N = 111)	18 (24.0) * 1 missing case	16 (43.2)	0.042
Hypocortisolism (N = 110)	26 (34.7) * 2 missing cases	16 (43.2)	0.437
Hyposomatotropism (N = 107)	16 (21.3) * 4 missing cases	16 (43.2) * 1 missing case	0.019
Hypogonadism (N = 103)	14 (18.7) * 6 missing cases	14 (37.8) * 3 missing case	0.025
Panhypopituitarism (N = 111)	14 (18.7) * 1 missing case	10 (27.0)	0.096
Diabetes insipidus (N = 112)	24 (41.5)	10 (27.0)	0.590
Previous treatments, n (%)			
Transcranial approach (N = 12)	6 (8.0)	6 (16.2)	0.734
Transsphenoidal approach (N = 2)	1 (1.3)	1 (2.7)	
Others (CSF diversion or ommaya reservoir insertion) (N = 9)	3 (4.0)	6 (16.2)	

Table 2. Tumor characteristics

Total (N = 112)	**TCA (N = 75)**	**TSA (N = 37)**	**P-value**
Recurrence prior to surgery			
Primary tumors	68 (90.7)	27 (73.0)	0.014
Recurred tumors	7 (9.3)	10 (27.0)	
Tumor size			
Maximum diameter (cm), Mean± SD *	4.29 ± 1.07	3.43 ± 1.35	<0.001
Volume (cm^3), Mean± SD *	26.1 ± 40.9	12.9 ± 10.8	0.061
Tumor classification			
Wang et al., 2005 [16]			
Subdiaphragmatic with intact diaphragm sellae (N = 43)	25 (33.3)	18 (48.6)	0.183
Supradiaphragmatic type (N = 53)	40 (53.3)	13 (35.1)	
Subdiaphragmatic with incompetent diaphragm (N = 16)	10 (13.3)	6 (16.2)	
Kassam et al., 2008 [6]			
Preinfundibular (N = 15)	3 (4.0)	12 (32.4)	< 0.001
Transinfundibular (N = 36)	25 (33.3)	11 (29.7)	
Retroinfundibular (N = 61)	47 (77.0)	14 (37.8)	
Liu et al., 2018 [17]			
Pituitary gland involvement (Q-CRP) (N = 43)	25 (33.3)	18 (48.6)	0.292
Pituitary stalk involvement (S-CRP) (N = 26)	19 (25.3)	7 (18.9)	
Tubero-infundibular involvement with subarachnoid location (T-CRP) (N = 43)	31 (41.3)	12 (32.4)	

Table 3. Surgical outcomes according to different types of tumor classification and degree of resection

Anatomical classification	Surgical approach	EOR		Adjuvant therapy	Visual change			CSF leakage	Infection	Postop hypothalamic dysfunction (cognitive and/or behavioral dysfunction)
		GTR	STR		Improved	No change	Deteriorated			
Wang et al., 2005 [16]										
Subdiaphragmatic with intact diaphragma sellae (N = 43)	TCA (25)	21	4	4	7	7	4	0	1	1
	TSA (18)	15	3	4	8	6	1	1	4	2
	P-value	1.000		0.701	0.431			0.419	0.144	0.573
Subdiaphragmatic with incompetent diaphragm (N = 16)	TCA (10)	5	5	5	3	1	3	0	1	4
	TSA (6)	6	0	1	1	1	2	0	3	2
	P-value	0.093		0.307	0.814			-	0.118	1.000
Supradiaphragmatic type (N = 53)	TCA (40)	29	11	9	12	8	15	1	0	7
	TSA (13)	11	2	6	4	4	3	0	5	4
	P-value	0.480		0.100	0.573			1.000	<0.001	0.432
Kassam et al., 2008 [6]										
Preinfundibular (N = 15)	TCA (3)	3	0	0	0	0	2	0	1	0
	TSA (12)	11	1	4	2	7	1	1	3	0
	P-value	1.000		0.516	0.027			1.000	1.000	-
Transinfundibular (N = 36)	TCA (25)	20	5	6	8	8	5	0	0	3
	TSA (11)	9	1	3	7	1	1	0	3	3
	P-value	1.000		1.000	0.134			-[b]	0.023	0.363
Retroinfundibular (N = 61)	TCA (47)	32	15	12	14	8	15	2	1	9
	TSA (14)	12	2	4	4	3	4	0	6	5
	P-value	0.311		1.000	0.923			1.000	<0.001	0.196
Liu et al., 2018 [17]										
Pituitary gland involvement	TCA (25)	20	5	5	7	7	4	0	1	2

(Q-CRP) (N = 43)	TSA (18)	15	3	4	8	6	1	1	4	2
	P-value	1.000		1.000	0.431			0.419	0.144	1.000
Pituitary stalk involvement (S-CRP) (N = 26)	TCA (19)	12	7	6	6	2	8	0	1	3
	TSA (7)	6	1	2	2	1	2	0	3	2
	P-value	0.375		1.000	0.889			-	0.047	0.588
Tubero-infundibular involvement with subarachnoid location (T-CRP) (N = 43)	TCA (31)	23	8	7	9	7	10	1	0	7
	TSA (12)	11	1	5	3	4	3	0	5	4
	P-value	0.405		0.211	0.743			1.000*	0.001	0.467

Table 4. Oncological outcome

Total (N = 112)	**TCA (N = 75)**	**TSA (N = 37)**	**P-value**
Duration of follow-up			
Months	127.1 ± 75.1	85.95 ± 62.8	0.003
Extent of resection			
Gross total resection (100%)	55 (73.3)	32 (86.5)	0.116
Subtotal resection (<100%)	20 (26.7)	5 (13.5)	
Pathology			
Adamantinomatous : Papillary	75:0	37:0	-
Residual tumor			
Residual tumor maximum diameter (cm) (N = 111)	0.27 ± 0.62 * 1 missing case	0.14 ± 0.34	0.145
Residual tumor volume (cm^3) (N = 111)	0.4 ± 1.5 * 1 missing case	0.04 ± 0.09	0.020
Major complications			
Mortality (N = 2)	2 (2.7)	0 (0)	1.000
Hemorrhage, infarction (N = 13)	8 (10.7)	5 (13.5)	0.658
Infection (N = 14)	2 (2.7)	12 (32.4)	<0.001
CSF leakage (N = 2)	1 (1.3)	1 (2.7)	1.000
Seizure (N = 9)	9 (12.0)	0 (0)	0.029
Adjuvant therapy			
Time between surgery and adjuvant therapy (months) (N = 23)	29.19 ± 32.07	19.57 ± 16.28	0.464
Radiation therapy (N = 12)	9 (12.0)	3 (8.1)	0.273
Radiosurgery (N = 17)	9 (12.0)	8 (21.6)	
Recurrence			
Recurrence (N = 35, 31.3%)	25 (33.3)	10 (28.6)	0.498
Time to recurrence (months), Mean± SD	19.92 ± 14.73	29.60 ± 17.63	0.106
Location of recurrence			
Sella (N = 20, 17.9%)	12 (16.0)	8 (21.6)	0.524
Optic chiasm (N = 5, 4.5%)	5 (6.7)	0 (2.7)	
Hypothalamus (N = 4, 3.6%)	3 (4.0)	1 (2.7)	
Third ventricle (N = 2, 1.8%)	2 (2.7)	0 (0)	
Pituitary stalk (N = 1, 0.9%)	0 (0)	1 (2.7)	
Others (frontal base, cerebellopontine angle, etc) (N = 4, 3.6%)	4 (5.3)	0 (0)	

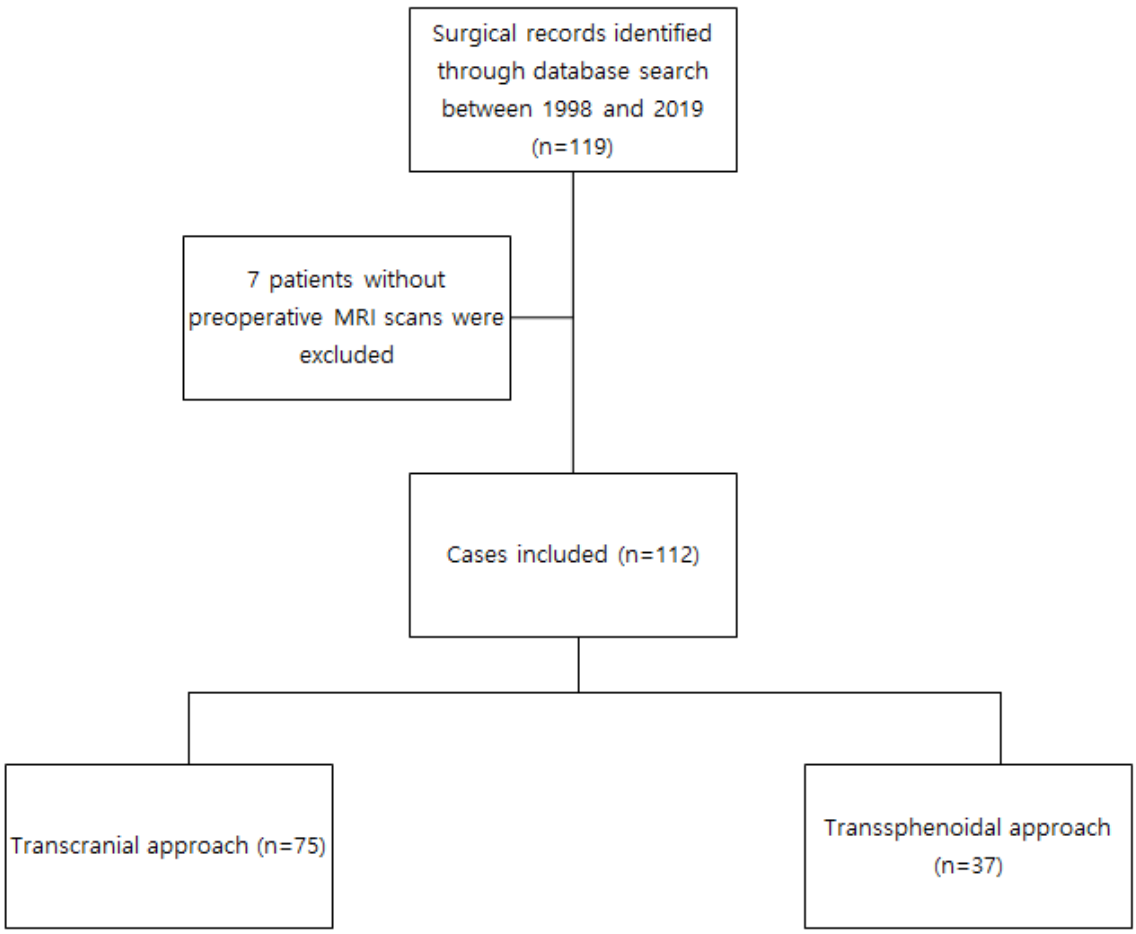
Table 5. Factors for recurrence in univariate and multivariate analyses

	Univariate			Multivariate		
Parameter	HR	95% CI	P-value	HR	95% CI	P-value
Extent of resection	0.20	0.10-0.40	<0.001	0.12	0.05-0.29	<0.001
Surgical approach	1.24	0.59-2.58	0.569	0.74	0.28-1.94	0.541
Tumor classification						
Wang et al., 2005 [16]						
Subdiaphragmatic with intact diaphragm sellae (N = 43)	1		0.173	1		0.479
Supradiaphragmatic (N = 53)	4.04	0.93-17.6	0.063	0.93	0.09-9.98	0.955
Subdiaphragmatic with incompenetn diaphragm sellae (N = 16)	3.2	0.74-13.85	0.120	4.94	0.37-66.18	0.227
Kassam et al., 2008 [6]						
Preinfundibular (N = 15)	1		0.761	1		0.515
Transinfundibular (N = 36)	0.80	0.27-2.36	0.689	0.85	0.13-5.72	0.865
Retroinfundibular (N = 61)	1.20	0.58-2.48	0.620	1.68	0.42-6.74	0.463
Liu et al., 2018 [17]						
Pituitary gland involvement (Q-CRP) (N = 43)	1		0.048	1		0.017
Pituitary stalk involvement (S-CRP) (N = 26)	1.17	0.59-2.35	0.652	6.28	0.22-180.59	0.284
Tubero-infundibular involvement with subarachnoid location (T-CRP) (N = 43)	0.25	0.07-0.87	0.029	0.20	0.04-0.96	0.045
Tumor volume	1.00	0.99-1.01	0.862	1.01	0.98-1.03	0.651
Tumor size	1.02	0.99-1.04	0.155	1.01	0.97-1.06	0.553
Primary or recurrent tumor	0.81	0.34-1.95	0.634	0.40	0.13-1.26	0.116

Table 6. Neuroendocrinological outcome

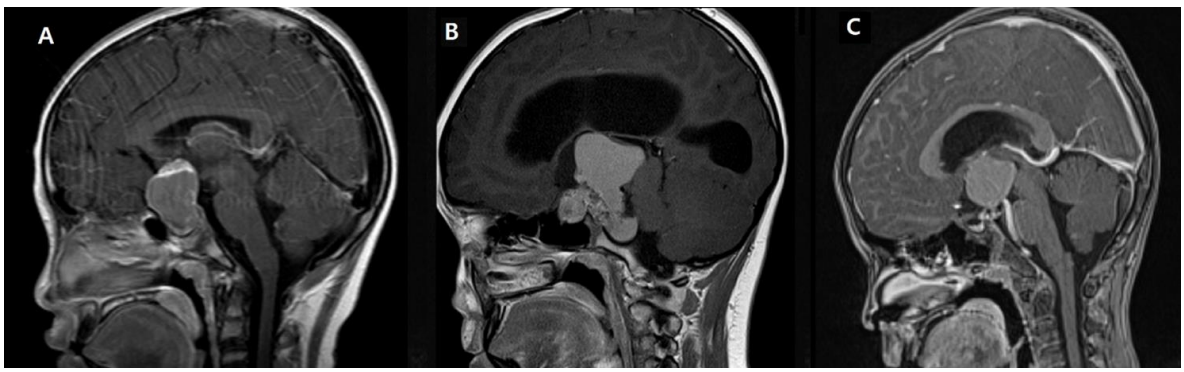
Total (N = 112)	**TCA (N = 75)**	**TSA (N = 37)**	**P-value**
Functional outcome			
KPS	78.3 ± 18.0	80.5 ± 19.9	0.544
mRS	1.9 ± 1.3	1.7 ± 1.4	0.380
Hypothalamic function outcome			
Puget grade [18]	1.7 ± 0.5	1.3 ± 0.8	0.005
Hypothalamic dysfunction (N = 20)	12 (16.0)	8 (21.6)	0.505
Cognitive dysfunction (N = 9)	5 (6.7)	4 (10.8)	0.813
Behavioral dysfunction (N = 4)	3 (4.0)	1 (2.7)	
Both cognitive and behavioral dysfunction (N = 7)	4 (5.3)	3 (8.1)	
Obesity (BMI >25) (N = 36)	24 (36.0)	12 (32.4)	0.925
BMI, Mean± SD	23.1 ± 5.7	23.1 ± 5.4	0.941
Ophthalmologic outcome (N=90, TCA=60, TSA=30), n (%)			
Improved (N = 35)	22 (29.3)	13 (35.1)	0.262
Stationary (N = 27)	16 (21.3)	11 (29.7)	
Deteriorated (N = 28)	22 (29.3) * 15 missing cases	6 (16.2) * 7 missing case	
Endocrinologic outcome (N=111, TCA=74, TSA=37), n (%)			
Improved (N = 0)	0 (0)	0 (0)	0.026 *
Stationary (N = 24)	11 (14.7)	13 (35.1)	
Deteriorated (N = 87)	63 (84.0) * 1 missing case	24 (64.9)	
Endocrinologic status (N=112), n (%) ‡			
Normal (N = 3)	0 (0)	3 (8.1)	0.096
Partial hypopituitarism (N = 5)	3 (4.0)	2 (5.4)	
Panhypopituitarism (N = 104)	72 (96.0)	32 (86.5)	
Diabetes insipidus (N = 102)	73 (97.3)	29 (78.4)	0.002 *

Figure 1. Flow diagram documenting case inclusion and exclusion process.



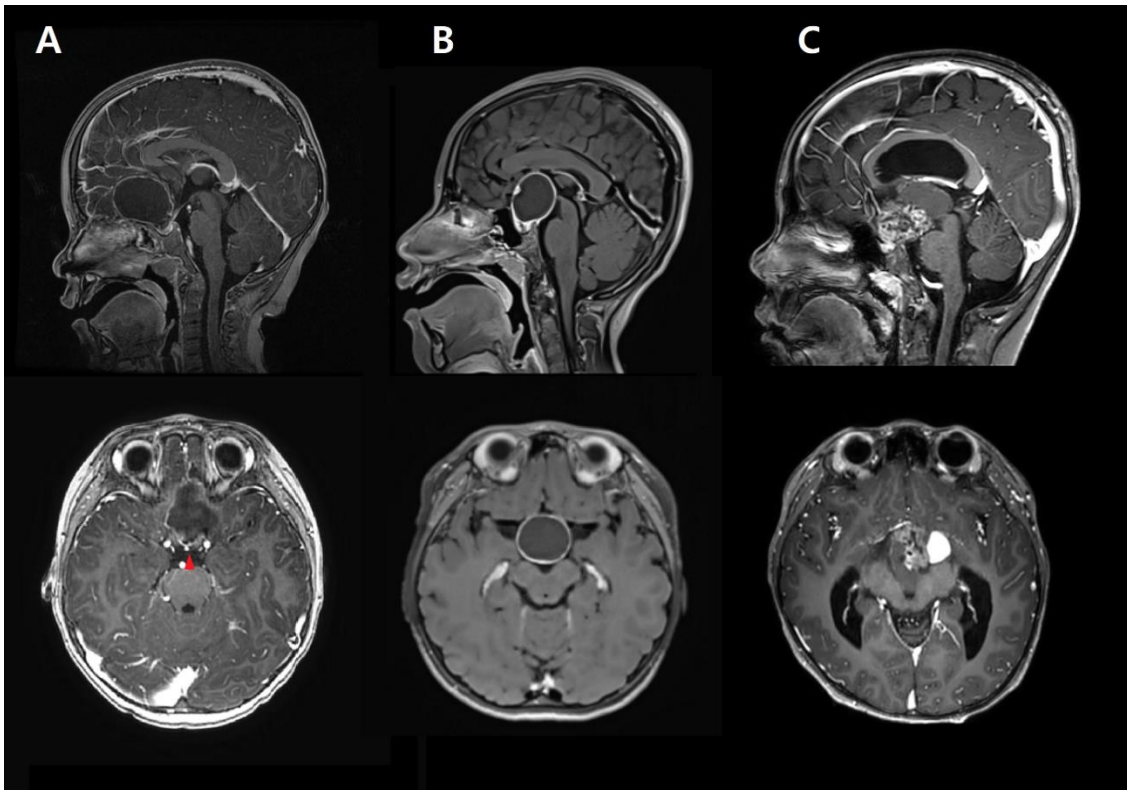
Flow diagram documenting case inclusion and exclusion process. Each group were further divided using different tumor classification methods.

Figure 2. Contrast-enhanced magnetic resonance (MR) imaging showing craniopharyngioma classification according to its location relative to the chiasm [16].



A. Subdiaphragmatic tumors with intact diaphragm sellae frequently arise below diaphragm sellae and the tumor is separated from the neurovascular structure by the diaphragm sellae. The chiasm is often elevated by the tumor.
B. Subdiaphragmatic craniopharyngioma with incompetent diaphragm sellae have an intrasellar origin and extend through the opening of the diaphragm sellae. The tumor is in direct contact with the supradiaphragmatic components as there is no diaphragm to intervene between the neurovascular structures and the tumor.
C. Supradiaphragmatic tumors. As they frequently lack subdiaphragmatic component, they extend in rostral direction towards the third ventricle and have an intact diaphragm sellae. The supradiaphragmatic tumors often grow into the cisternal space.

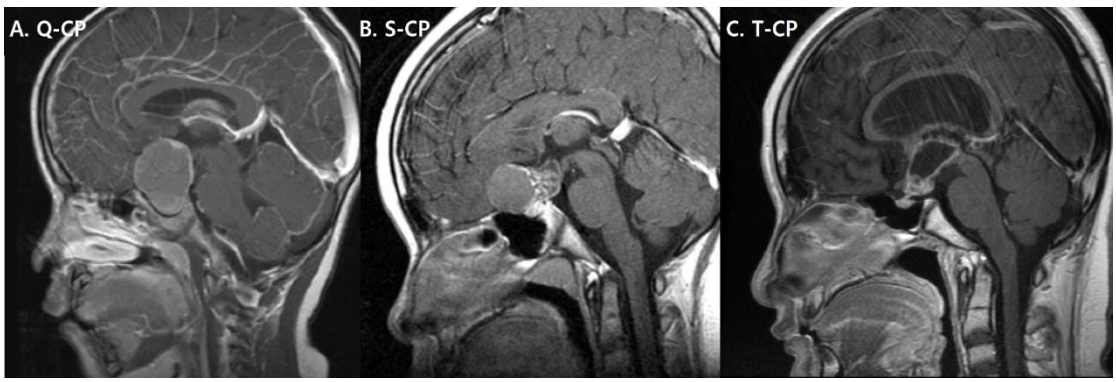
Figure 3. Contrast-enhanced magnetic resonance (MR) images displaying craniopharyngioma classification according to its relationship with the infundibulum [6]



A. Preinfundibular type craniopharyngioma showing tumor situated anterior to the infundibulum. Axial images display infundibulum located posterior to the tumor noted with a red arrowhead. The tumor typically extends into the prechiasmatic cistern.
B. Transinfundibular type craniopharyngioma. The sagittal MR image displays widening of the pituitary stalk. The widened stalk and the tumor spreads retrochiasmatically and displaces the chiasm anteriorly.

C. Retroinfundibular type craniopharyngioma. The tumor is located in the retrochiasmatic and retroinfundibular space, and the pituitary stalk is challenging to visualize as it is thinned and attenuated. The tumor may grow superiorly to invade the anterior third ventricle (Type IIIa) or may progress caudally towards the interpeduncular fossa (Type IIIb)

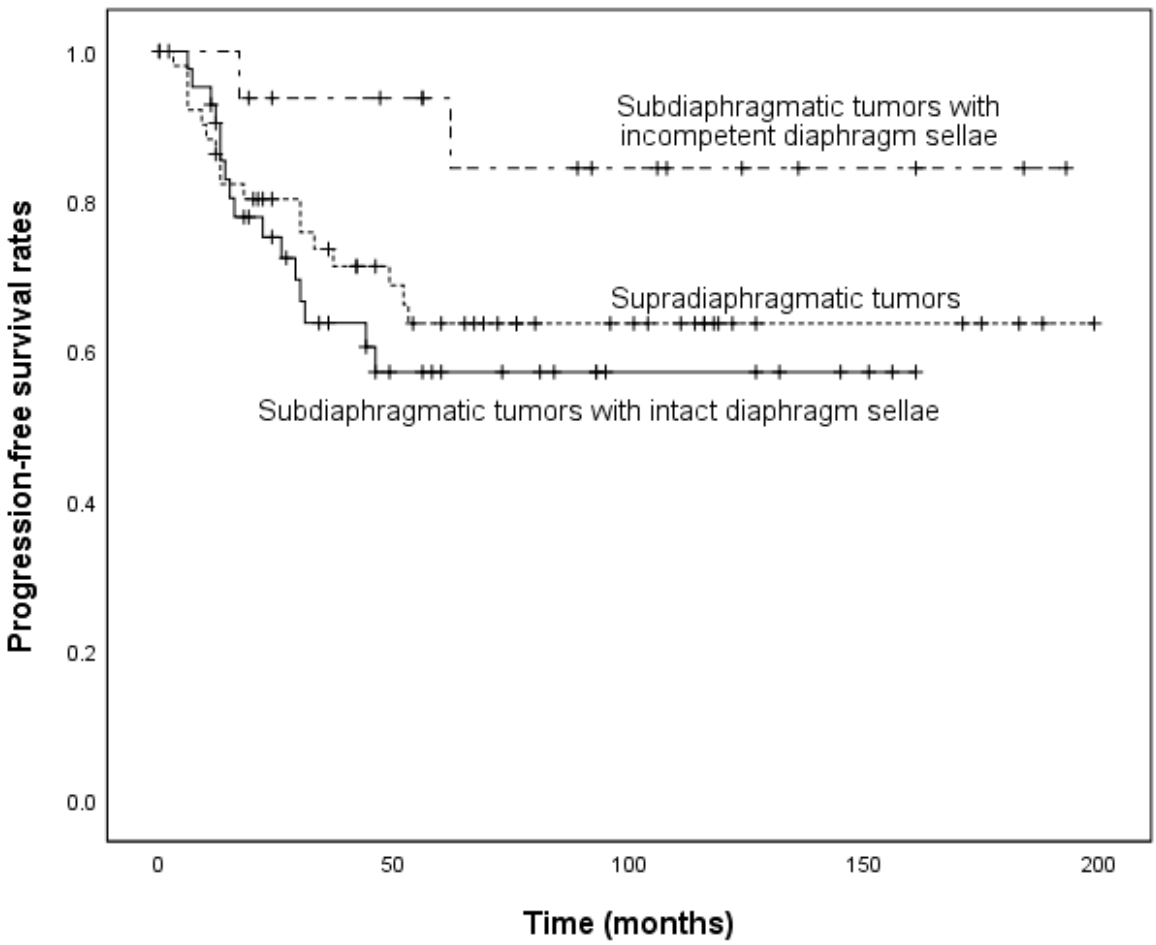
Figure 4. Contrast-enhanced magnetic resonance (MR) images showing craniopharyngioma classification according to the main tumor location [17]



Contrast-enhanced magnetic resonance (MR) images showing craniopharyngioma classification according to the main tumor location [17]

A. Craniopharyngiomas with pituitary gland involvement (Q-CRPs): occur in the subdiaphragmatic space and have adhesions with the pituitary gland.
B. Craniopharyngiomas with pituitary stalk involvement (S-CRPs): arise in the low-to middle portion of the infundibulum.
C. Craniopharyngiomas with tubero-infundibular involvement (T-CRPs): originate from the pars tuberalis and are in the subarachnoid location; they frequently invade the third ventricle.

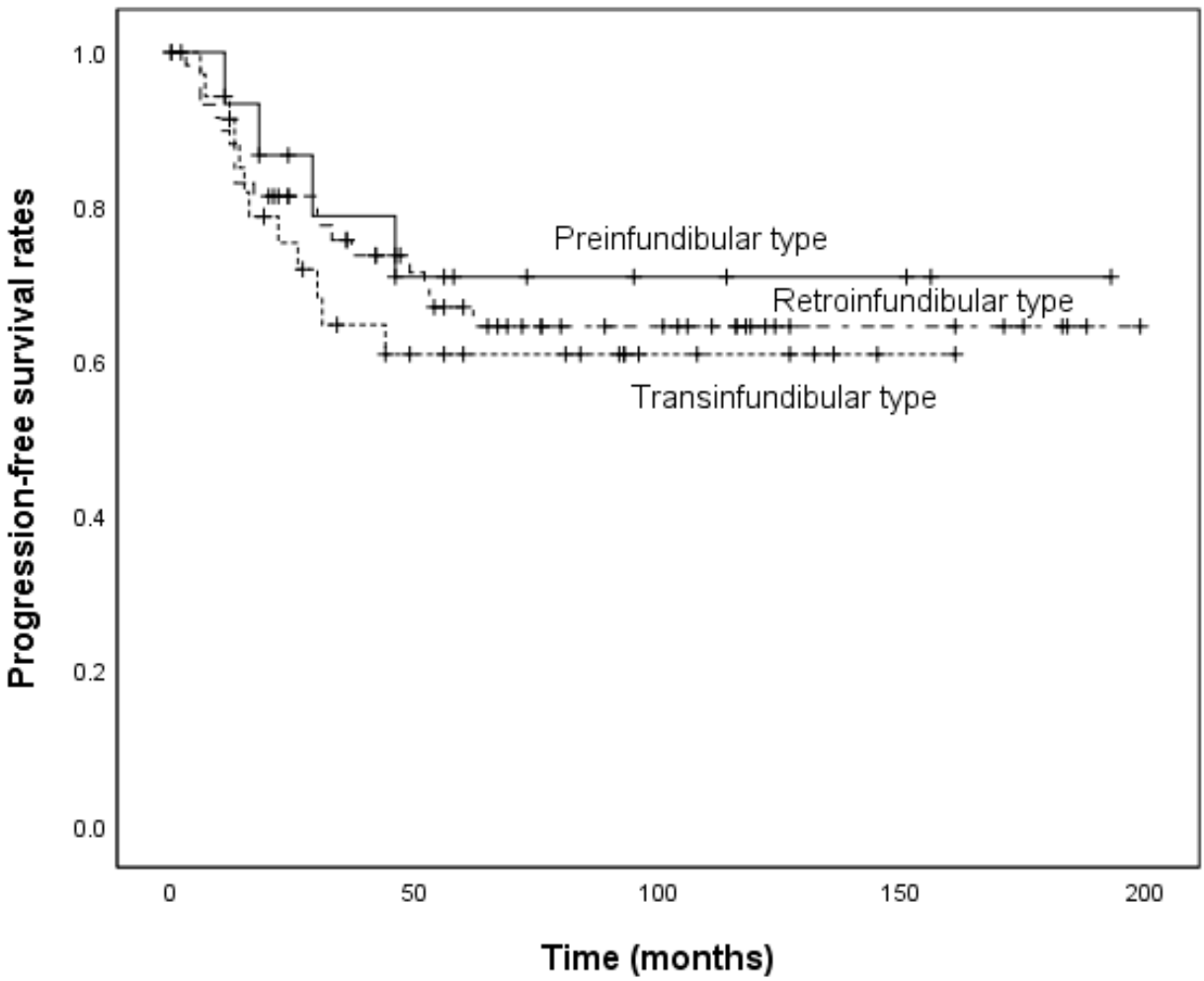
Figure 5. Kaplan-Meier curves comparing progression-free survival rates between groups divided by tumor relationship with the diaphragm sellae.



Kaplan-Meier curves comparing progression free survival rates between groups defined by tumor relationship with the diaphragm sellae [16].

Subdiaphragmatic tumors with incompetent diaphragm showed a trend for longer progression-free survival compared with the other two tumor types. However, the difference was not statistically significant. (Log-rank test P-value = 0.135)

Figure 6. Kaplan-Meier curves comparing progression free survival rates between groups defined by tumor relationship with the infundibulum



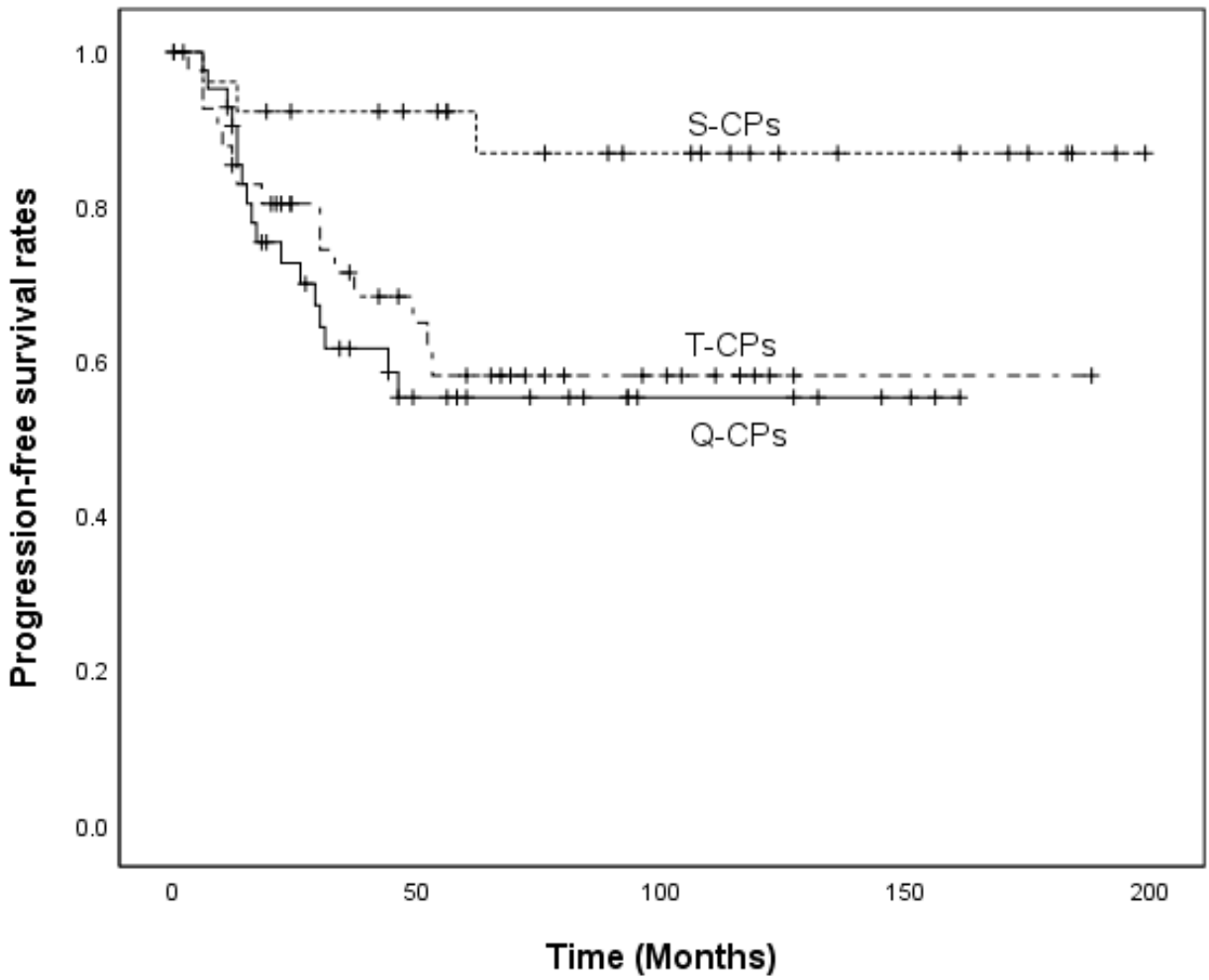
Kaplan-Meier curves comparing progression free survival rates (PFS) between groups defined by tumor relationship with the infundibulum [6].

Preinfundibular type craniopharyngioma are situated anterior to the infundibulum and typically extends into the prechiasmatic cistern. Transinfundibular type craniopharyngioma displays widening of the pituitary stalk and the tumor spreads retrochiasmatically and displaces the chiasm

anteriorly. Retroinfundibular type craniopharyngioma is located in the retrochiasmatic and retroinfundibular space, and the pituitary stalk is thinned and attenuated. The tumor may grow superiorly to invade the anterior third ventricle (Type IIIa) or may progress caudally towards the interpeduncular fossa (Type IIIb)

The PFS between preinfundibular, transinfundibular and retroinfundibular tumors did not show statistically significant differences (Log-rank test P = 0.757)

Figure 7. Kaplan-Meier curves comparing progression free survival rates between groups differentiated by main tumor locations

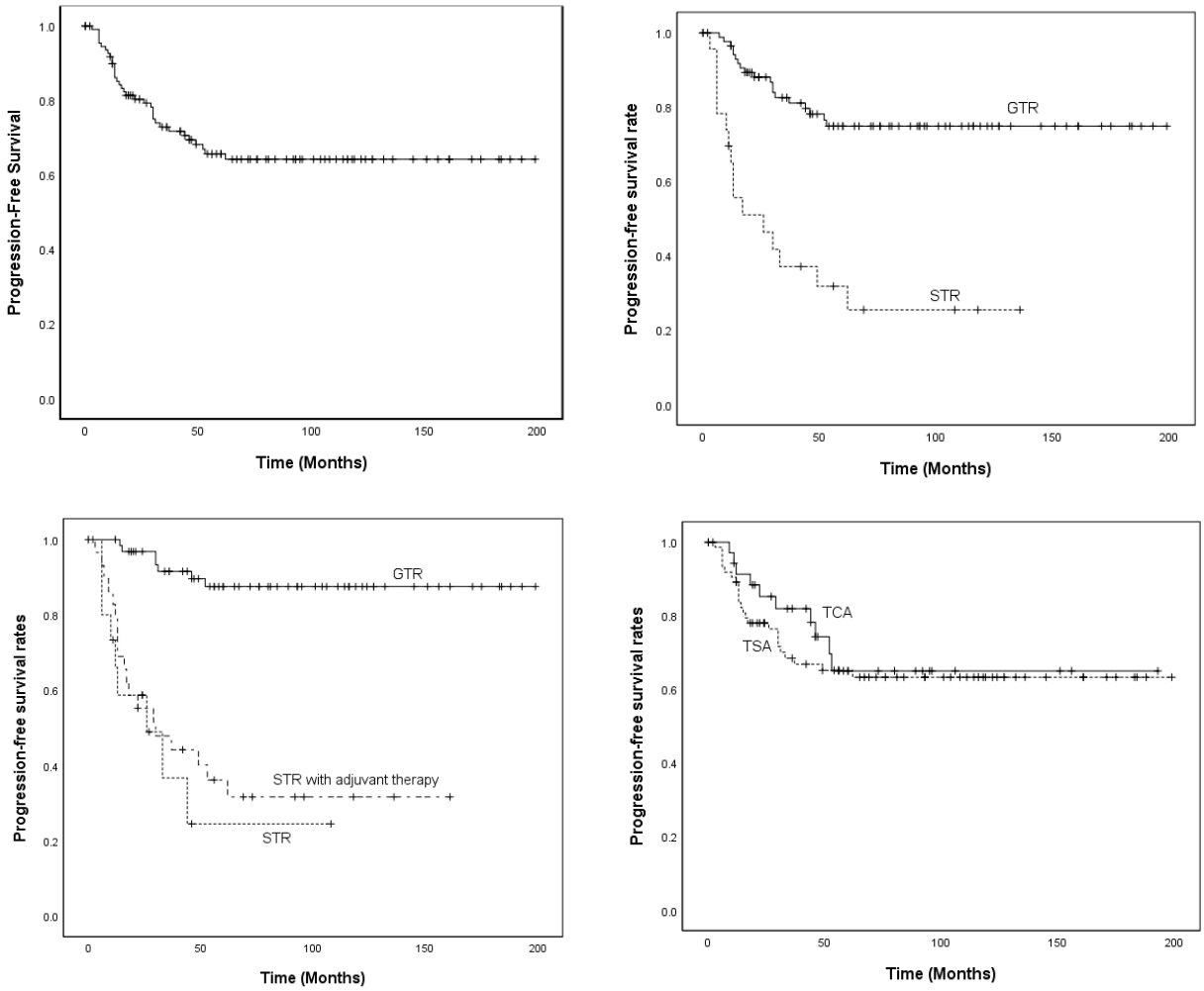


Kaplan-Meier curves comparing progression free survival rates between groups differentiated by main tumor locations [17].

Craniopharyngiomas with pituitary gland involvement (Q-CRPs) occur in the subdiaphragmatic space and have adhesions with the pituitary gland. Craniopharyngiomas with pituitary stalk involvement (S-CRPs) arise in the low-to middle portion of the infundibulum. Craniopharyngiomas with tubero-

infundibular involvement (T-CRPs) originate from the pars tuberalis and are in the subarachnoid location; they frequently invade the third ventricle. Patients with S type craniopharyngiomas displayed a longer progression free survival than the other two groups that was statistically significant (Log rank test $P = 0.027$)

Figure 8. Kaplan-Meier progression-free survival curve of patients undergoing surgical resection for craniopharyngioma.



A. Kaplan-Meier progression-free survival curve of patients who received surgical resection for craniopharyngiomas. 5-year progression-free survival: 64%, median time to progression: 31 months

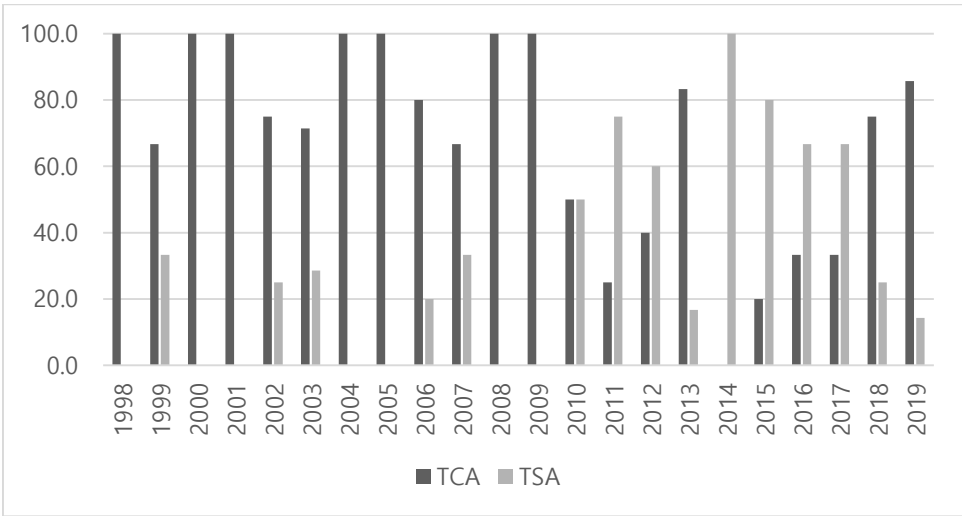
B. Kaplan-Meier curves comparing the progression-free survival rates for patients who underwent gross total resection (GTR) and subtotal

resection (STR). Median time to recurrence were 21 months for the GTR group and 13 months for the STR group. The two groups displayed a significantly different progression-free survival, with Log rank (Mantel-Cox) P <0.001

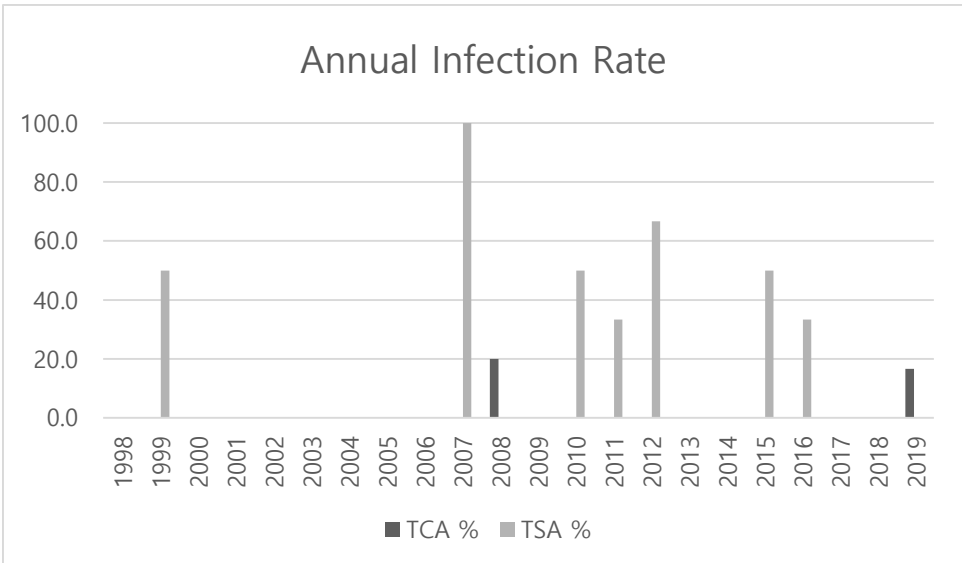
C. Kaplan-Meier curves comparing the progression-free survival rates for patients who received gross total resection (GTR, 100% resection), subtotal resection (STR, <100% resection) and subtotal resection with adjuvant therapy. The PFS of STR group and STR with adjuvant therapy were comparable. The GTR group showed a significantly longer progression-free survival compared to the other two groups (P<0.001)

D. Kaplan-Meier curves comparing progression-free survival rates (PFS) for patients undergoing transcranial approach (TCA) versus transsphenoidal approach (TSA) for craniopharyngioma. The PFS did not statistically differ between the TCA and the TSA groups. (Log rank test P = 0.566)

Figure 9. Bar graphs displaying annual percentages of surgical approaches and infection rates

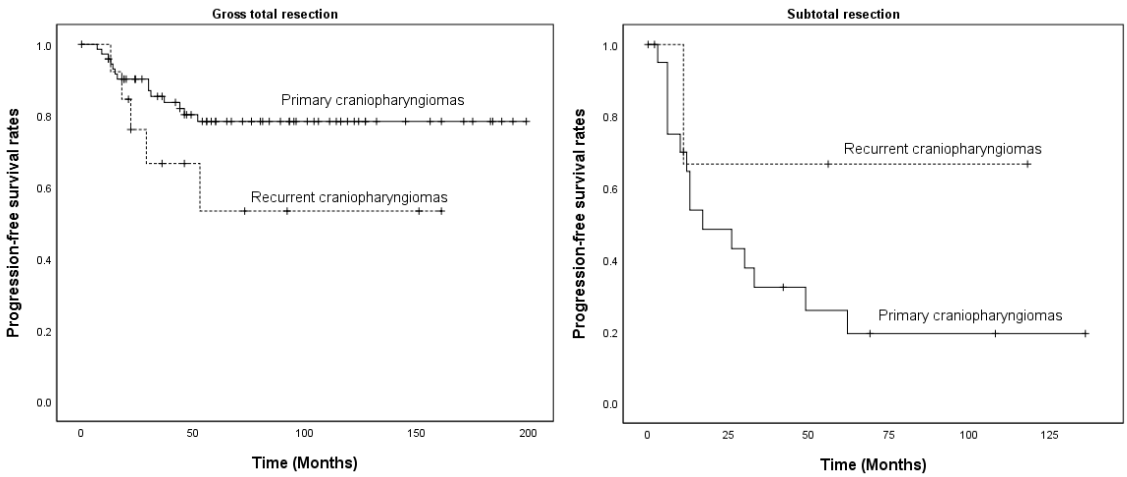


A. Bar graph displaying percentage of cases treated with transcranial approach (TCA) versus transsphenoidal approach (TSA) between 1998 and 2019.



B. Bar graph showing annual percentage of post-operative infections in the TCA and the TSA groups

Figure 10. Kaplan-Meier curves comparing progression-free survival rates between patients with primary and recurred tumors.

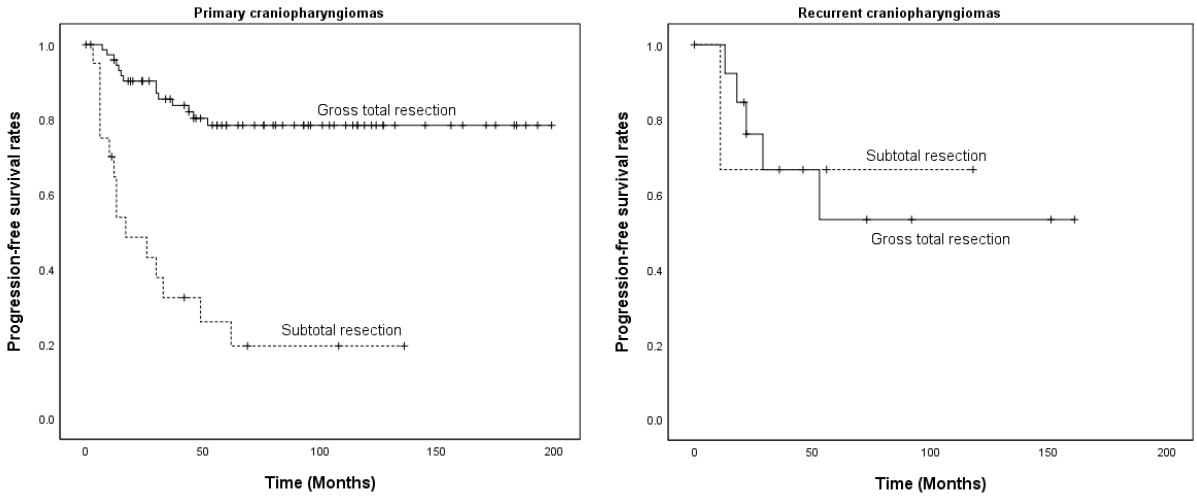


A. Kaplan-Meier curves comparing progression-free survival rates (PFS) between patients with primary and recurred tumors. Primary craniopharyngioma group included patients with primary tumors undergoing initial resection at our institution, and Recurrent tumor group included patients who underwenet surgical resection for recurrent craniopharyngioma. The PFS difference between the two groups that underwent gross total resection were not statistically significant (Log-rank test P-value = 0.096), but the two groups displayed a clear trend with patients in primary craniopharyngiomas experiencing longer PFS.

B. Kaplan-Meier curves comparing progression-free survival rates (PFS) between patients with primary and recurred tumors. Primary

craniopharyngioma group included patients with primary tumors undergoing initial resection at our institution, and Recurrent tumor group included patients who underwenet surgical resection for recurrent craniopharyngioma. The PFS difference between the two groups that underwent subtotal resection were not statistically significant. (Log-rank test P-value = 0.245)

Figure 11. Kaplan-Meier curves comparing progression-free survival rates between patients with primary and recurrent tumors stratified by the extent of resection.



A. Kaplan-Meier curves comparing progression-free survival rates (PFS) between patients undergoing gross total resection (GTR) and subtotal resection (STR) for craniopharyngioma, stratified by the presence of previous recurrences. In the primary tumor group, PFS between GTR and STR groups showed a statistically significant difference (Log-rank test P-value < 0.001)

B. Kaplan-Meier curves comparing progression-free survival rates (PFS) between patients undergoing gross total resection (GTR) and subtotal resection (STR) for craniopharyngioma, stratified by the presence of previous recurrences. In the recurrent tumor group, patients with history of prior craniopharyngioma resection at local

clinics and undergoing surgery for recurrence at our institution did not show a statistically significant difference in PFS between GTR and STR groups (Log-rank test P-value = 0.902)

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Abstract

연구목적: 소아 두개인두종의 치료에 있어 경접형동 접근법과 개두술의 결과를 비교 분석하는 것을 목표로 한다. 그리고 경접형동 접근법과 개두술의 결과가 두개인두종의 3개의 해부학적 종양 분류에 따라 차이가 나는지 조사하고자 한다. 재발을 예측하는 인자를 재평가하고 목표이다.

연구방법: 1998부터 2019 년 사이 서울대학교 어린이병원에서 두개인두종에 대하여 수술적 치료를 받은 20세 미만 환자를 대상으로 한다. 환자의 의무기록을 후향적으로 검토하여 수술 전, 후 상태, 종양의 특성, 합병증 여부를 분석한다. 환자는 경접형동 접근법과 개두술 군으로 나누었으며, 각 군 마다 3개의 해부학적 종양 분류를 사용하여 아형을 나누었다. 각 군 간의 무진행상존율을 비교하기 위하여 카플란-마이어 곡선을 사용하였고, 종양 진행의 위험인자를 확인하기 위해 콕스 회귀 모형을 사용하였다.

결과: 1998년부터 2019년 사이 총 112명의 환자가 수술적 치료를 받았으며, 그 중 75명은 개두술을, 37명은 경접형동 접근법으로 치료받았다. 전체 코호트에 대한 5년 무진행생존 기간은 64 ± 5% 였다. 두 수술법에 따른 종양 절제 범위 (P = 0.116), 무진행생존 (P = 0.566) 및 재발률 (P = 0.498) 의 차이는 없었다. 각 종양 아형에서 경접형동 접근법 및 개두술 그룹 간 결과는 유사하였다. Subdiaphragmatic type with competent diaphragm sellae 의 두개인두종에서 경접형동 접근법을 사용하였을 시 시력 및 시야 호전이 더 많은 것으로 나타났다 (P = 0.027). 무진행생존율의 예측인자로는 절제 범위 (HR 0.12, 95 % CI 0.05-0.29, P <0.001) 및 안장가로막 하 종양의 유무 (P = 0.017) 이 통계학적으로 유의하게 나타났다.

결론: 두개인두종의 모든 해부학적 아형에서 경접형동 접근법은 소아 두개인두종의 치료에 있어 개두술 만큼 안전하고 유용한 수술법이다. Subdiaphragmatic type with competent diaphragm sellae 에서는 경접

형동 접근법이 개두술에 비하여 시력 회복이 좋은 것으로 나타났다. 종양의 위치가 시신경교차 후방에 있는 경우에도 경접형동 접근법이 효과가 있다. 현재로써 종양의 재발을 막는 가장 강력한 방법은 종양의 전절제이며, 안장가로막 하 종양이 존재할 시 재발률이 더 높았다.