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CLINICAL ARTICLE

Intraventricular craniopharyngioma: morphological analysis and outcome evaluation of 17 cases

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Abstract
Purpose There is still some confusion with regard to the tumor–third ventricle floor (3rd VF) relationship of craniopharyngiomas located exclusively within the third ventricle. This study aims to provide some evidence to clarify the growth pattern of intraventricular craniopharyngiomas (IVC), and to summarize the surgical strategy and outcome.
Methods Seventeen cases of IVC were reviewed retrospectively in relation to preoperative imaging, clinical presentation, intraoperative findings, tumor pathology, and surgical outcome. The tumor–3rd VF relationship and the tumor's stratification were analyzed based on intraoperative inspection and histology.
Findings Variable adherence patterns of IVC to the 3rd VF were found, which were classified as (a) purely IVC with pedicle attachment to 3rd VF (two cases), (b) intra-3rd VF tumors with wide-based attachment but a dissectible tumor boundary (seven cases), and (c) intra-3rd VF tumors with an undissectible wide, tight attachment (eight cases). Histological analysis revealed that both of the two cases with growth pattern "a" intruded into the third ventricular cavity without a covering layer of neural tissue (which only exists in the squamous-papillary subtype). Tumors with growth pattern "b" and "c," in contrast, were noted to have a thin layer of neural tissue. This occurred in both subtypes (11 adamantinomatous, 4 papillary). Total removal was accomplished in all tumors demonstrating growth pattern "a" and "b." There was also better preservation of the 3rd VF and consequently a better outcome. On the other hand, total removal was only achieved in 50% of tumors showing growth pattern "c" including one mortality. No recurrence has been encountered in patients whose tumors were totally removed.
Conclusion Variable adherence patterns and tumor subtypes were observed in IVCs, which were correlated to the tumor pathology, resectability, and subsequent prognosis.

Keywords Histology · Intraventricular craniopharyngiomas · Neurosurgery · Third ventricle floor

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Introduction

It is believed that adamantinomatous craniopharyngiomas (CPs) originate from the residual cells of Rathkes' pouch, located along the path from the nasopharynx to the infundibulum [1, 2]. The squamous-papillary subtype of CP, on the other hand, is thought to be the result of squamous metaplasia within the pars tuberalis of the pituitary gland [2, 3]. Considering these hypotheses, it seems that the neural parenchymal layer of the third ventricular floor (3rd VF) should be found at the superior aspect of the CP, separating the tumor and the third ventricular cavity. Tumors exclusively located within the third ventricle chamber (observed at autopsy or intraoperatively) have been extensively characterized [4–12]. This topographical location challenges the theory of origin of CPs, and also leads many neurosurgeons to pursue their true morphological features and diagnostic criteria [8, 13].

Following careful review of the literature, most of the reported intraventricular craniopharyngiomas (IVCs) were noted to have been diagnosed based on preoperative magnetic resonance imaging (MRI). Diagnostic proof was determined as their intraventricular location [5, 6, 8, 14, 15]. Pascual [16] analyzed all previously

reported IVCs and in 2004 proposed two hypothetic growth modes—primary and secondary. Secondary IVCs were thought to be the result of invasion from suprasellar CPs. These two growth modes were referred to as "strictly" IVC (primary) and "nonstrictly" IVC (secondary). An intact 3rd VF identified on pre- or postoperative MRI or from intraoperative impression was the diagnostic criterion for "strictly IVCs." Pascual also indicated that the "strictly IVC" (sIVC) subtype was associated with better postoperative outcome.

Following retrospective review of 195 cases of CP patients presenting in our hospital over a 12-year period, 17 cases were identified having an exclusive ventricular location. Through systematic analysis of the imaging, intraoperative findings, and outcome from long-term follow-up, these 17 cases were found to show variable tumor–3rd VF relationships. This variance in turn directly correlated to surgical resection and protection of the 3rd VF. In this study, we focus on the morphological features of IVCs, clinical presentations, and surgical outcome.

Clinical material and methods

From January 1997 to January 2009, 17 cases of IVC were identified from the 195 cases of CPs (19 papillary, 176 adamantinomatous) using the following inclusion criteria: (1) primary surgery, (2) intraventricular location of the tumor (i.e., a patent suprasellar cistern and an intact pituitary stalk on preoperative MRI), and (3) no tumor extension into the subarachnoid cistern noted intraoperatively (aside from a frog-belly-shaped inflation of the 3rd VF). In all, the diagnosis of CP was confirmed on histology. Squamous-papillary subtype of tumor was confirmed using previously established criteria [17].

Patient population and clinical manifestation

There were 2 pediatric cases (1 boy, 7 years old and 1 girl, 5 years old) and 15 adults (12 male, 3 female). The average age at time of surgery ranged from 7 to 55 years (mean 37.3±14.3). With regard to clinical presentation, 64.7% (11/17) had symptoms of raised intracranial pressure, and 47.1% had (8/17) cognitive disturbances (disorientation, confusion, apathy, delirium, and memory disturbances). Visual deficits (47.1%, 8/17) and diabetes insipidus (17.6% 3/17) were noted to be of lower incidence than in patients who had suprasellar CP [18–20]. Somnolence was found in 17.6% (3/17). The commonest etiology of this was hydrocephalus secondary to tumor. Growth retardation was noted in both the pediatric cases, one of which was further complicated by the additional presence of epilepsy.

Endocrine evaluation

Endocrine evaluation included pre- and postoperative measurement of basal serum levels of adrenocorticotropic hormone (ACTH), growth hormone (GH), prolactin (PRL), thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), cortisol, free T4, thyroxine, testosterone/estradiol, and progesterone (according to gender). Provocation testing was performed as necessary. Insulin (0.1 U/kg) and thyroid-releasing hormone (TRH; 500 U) were administered intravenously for provocation testing of cortisol, GH, and TSH. The somatotrophic axis was not evaluated in two patients due to clinical morbidity.

Hormone axis dysfunction was identified using the following criteria: corticotrophic axis: (1) a baseline plasma cortisol level less than 100 nmol/L or a peak value of plasma cortisol less than 500 nmol/L following an insulin stimulation test; somatotrophic axis: (1) children manifesting delayed growth and short stature or (2) a GH peak value less than 8 ng/mL following an insulin stimulation test; thyrotrophic axis: a plasma thyroxine or free T4 level less than normal or a TSH level following provocation of less than 10 mU/mL; gonadotrophic axis: clinical features of sexual dysfunction or amenorrhea and decreased serum testosterone (in males) or a diminished or undetectable progesterone and estrogen (for females).

GH deficiency was identified in 9 patients and hyperprolactinemia in 15 patients (31.1±12.1, from 16.5 to 66.8 mmol/L). As shown in Table 1, assessment of anterior pituitary function showed hypoadrenalism in 8 patients, hypothyroidism in 6, and hypogonadism in 14 of the 15 adult patients. Three patients (17.6%) had panhypopituitarism.

Neuroradiological findings

Preoperative MRI and computed tomography (CT) were available in all cases. The average diameter (defined as the longest axis) of the tumors was 3.2±0.7 cm (range 2.2–4.5 cm). Solid tumor was found in 6 cases (35.3%), and 11 were cystic and/or mixed tumors (64.7%). Solid tumors and the wall of cystic tumors were noted to demonstrate contrast enhancement on Gd-DTPA MRI.

Nine cases (52.9%) demonstrated calcification on CT, and 52.9% (9/17) were associated with hydrocephalus. This was severe in 17.6% (3/17) and moderate in 35.3% (6/17). Preoperative MRI revealed the 3rd VF in four cases (23.5%). The 3rd VF remained unidentified in 13 cases (76.5%) due to compression and distortion secondary to tumor.

Treatment strategy and approach selection

All the tumors were removed via the trans-lamina terminalis route with the aim of total resection. The microscope

Table 1 Preoperative endocrinological evaluation of the 17 cases of IVC

	Hypo-pit-adrenal axis	Hypo-pit-GH axis	Hypo-pit-thyroid axis	Hypo-pit-gonadal axis	Panhypopituitarism
Normal	9	8	11	1	14
Impaired	8	9	6	14	3
Total	17	17	17	15[a]	17

[a] Two children were excluded from evaluation of gonadal function

was used in all cases operated on by the senior author (Dr. Songtao Qi). The lamina terminalis (LT) was accessed through the medial aspect of a frontotemporal approach in 41% (7/17) patients and via an anterior interhemispheric approach in 59% (10/17). One case required external ventricular drainage due to severe hydrocephalus. In all patients, radiotherapy was deemed to be an option for adjunctive treatment, but not primary treatment.

Morphological analysis

To verify IVC relationships with the 3rd VF, we reviewed and analyzed preoperative MRI, surgical records, and videotapes of each patient retrospectively (Dr. Jun Pan and Yuntao Lu).

In eight cases, a square of tumor roof was resected following opening of the LT. Stratification of IVC was carried out using histological findings.

Outcome evaluation

All patients except one underwent long-term follow-up. This case was a mortality in the postoperative period. The average follow-up period was 46.8±23.8 months (range 14–117 months). Outcome was determined using the system of Fahlbusch et al. [19]: good (without any new permanent neurological, neuropsychological, or endocrine deficit); moderate (with new endocrine deficits requiring permanent replacement therapy); fair (with neurological or neuropsychological deficits but with autonomy); poor (severe neurological and/or hypothalamic disturbances with total dependency); or death.

For each pediatric patient, the body mass index (BMI) was calculated and recorded. They were then determined to be of normal weight, overweight (1 SD), or obese (≥2 SD) according to reference values for Chinese children [21].

Results

Surgical findings

LT and anterior communicating artery complex The tumors were exposed either by opening the anterior part of the LT (located between the optic chiasm and the anterior communicating artery (AcoA)) or by opening the deep upper posterior part of LT through the bilateral A2 space. In seven cases, the AcoA was divided to allow sufficient exposure.

Stratification of tumor surface After opening the LT, the upper surface of the tumor was carefully inspected. A stretched neural tissue layer (though extremely thin in most cases) covering the tumor surface was noted in 15 cases. Internal decompression and dissection of the interface between the lateral hypothalamic wall and tumor capsule were carried out only after this layer was incised. In the two solid tumors, the tumor appeared to be located within the ventricular cavity with an unidentifiable, extremely thin, membrane-like layer covering.

Tumor adherence patterns The tumors displayed variable adherence patterns in relation to the 3rd VF. These were described as follows (Figs. 1, 2, and 3): (a) pedicle attachment (2 cases)—tumor only attached to the anterior part of the 3rd VF at the infundibulum; the walls and posterior part of the 3rd VF remained intact without adherence; the 3rd VF was intact following total tumor removal; (b) wide attachment but dissectible tumor boundary (7 cases)—the tumor had a wide attachment to the third ventricle wall but could be safely dissected from the parenchyma allowing tracing of the tumor capsule following adequate debulking; the continuity of the 3rd VF could be preserved after total tumor removal but with membranous attenuation; and (c) wide tight attachment (8 cases)—separation of the tumor from the 3rd VF was quite difficult due to tight adherence of the tumor to the wall, necessitating sacrifice of the parenchyma to complete the removal.

Histological study

Pathologic study confirmed 11 cases of adamantinomatous CPs and 6 cases of papillary CPs. Over one third (6/17) of cases were of the papillary subtype, which comprised nearly one third of our 19 papillary tumors (out of a total of 195 cases of CPs), suggesting predilection of the papillary CPs to the third ventricle.

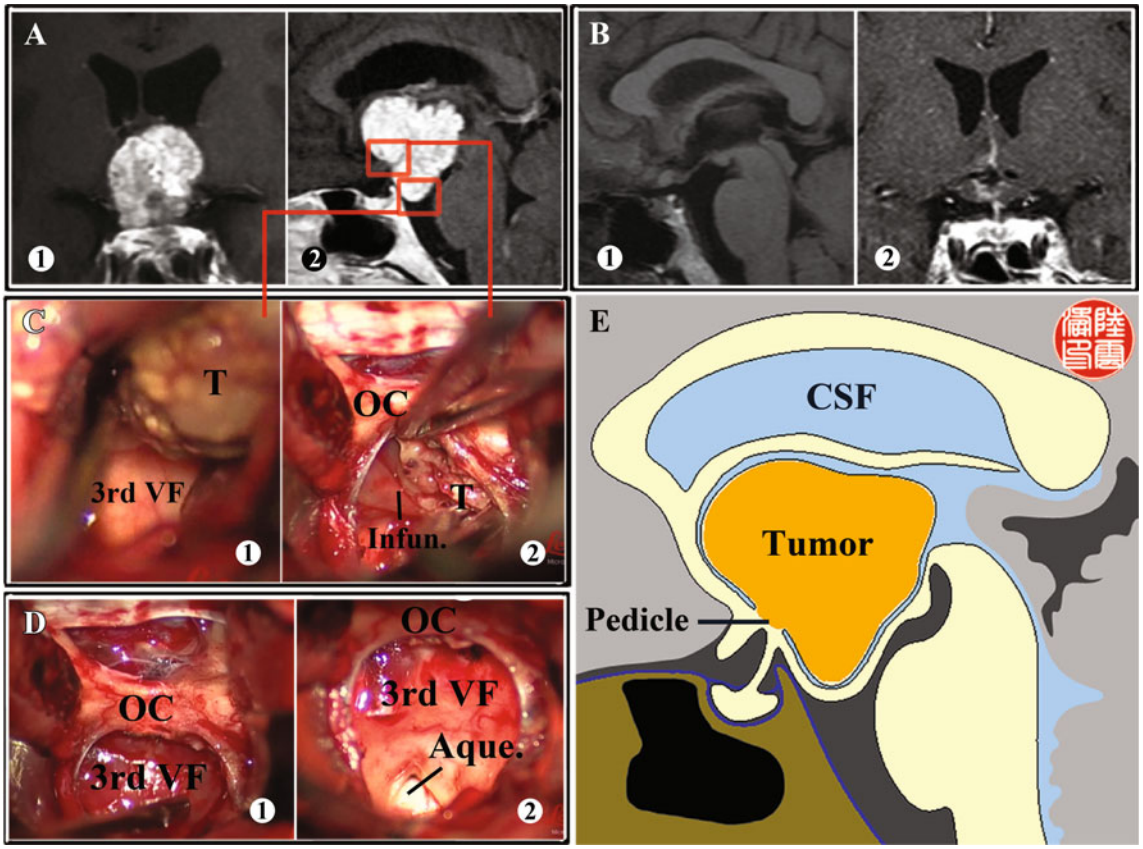

Fig. 1 Showing tumor adherence pattern "a" to the 3rd VF. **a** Presurgical MRI scan (① coronal; ② sagittal). **b** Postsurgical MRI scan (① Sagittal; ② Coronal). **c** Intrasurgical findings. A significant interface between tumor and third ventricular walls can be identified in the bilateral and posterior side (①). While at the pedicle side (②), tumor tightly adherent to the tuberoinfundibular part. **d** After tumor removal, intact 3rd VF and bilateral walls were found through the opened LT (① and ②). And the aqueduct of midbrain was observed (②). **e** The schematic diagram of the tumor's growth pattern "a" (*blue area* CSF. Tumors purely located inside the ventricular cavity with only a pedicle attached to the 3rd VF. Additionally, a potential ventricular space had been noted between tumor and ventricular walls). *OC* optical chiasm, *T* tumor, *Infun.* infundibulum, *Aque.* aqueduct of midbrain

Hematoxylin and eosin (H&E) stain of the square histological mass (eight cases) of the tumor's roof showed two kinds of tumor stratifications: (1) In the two cases with pattern "a" adherence to the 3rd VF, tumors intruded into the third ventricular cavity without being covered by a neural tissue layer or ependymal cell layer (the histological type of which was both papillary—Fig. 4, type I); and (2) In the other six cases with wide attachment to the 3rd VF, the tumor was still covered by a thin layer of neural tissue. Ependymal cells were noted in some regions. Typically, the cystic wall of the IVC was composed of an outer area of gliosis and an inner layer of adamantinomatous cells (Fig. 4, type II).

Correlation between the patterns of adherence, preoperative MRI, and tumor's pathology

Correlation between the adherence patterns to the 3rd VF and preoperative MRI was studied (Table 2). All four cases with identifiable 3rd VF on preoperative MRI had a variable degree of adherence (three of pattern "b" and one of pattern "c") noted intraoperatively. However, among the other 13 cases with unidentified 3rd VF on preoperative MRI, 2 cases proved to have only pedicle attachment to the 3rd VF (pattern "a"). Further pathologic study confirmed that both these two tumors were solid and were of the papillary subtype.

Correlation between the adherence patterns observed and tumor pathology were investigated (Table 2). All 11 cases of adamantinomatous CPs have pattern "b" or "c" of adherence to the 3rd VF, while the papillary CPs have a more variable adherence patterns to the 3rd VF.

Extent of removal

The surgeon's intraoperative impression of quality of removal was noted as well as MRI scans during 1–6 months postoperatively. In this cohort, 13 tumors were totally resected. In the other four cases, a small residual was left adherent to the 3rd VF due to tight adherence or the absence of a clear plane of dissection (considered to be

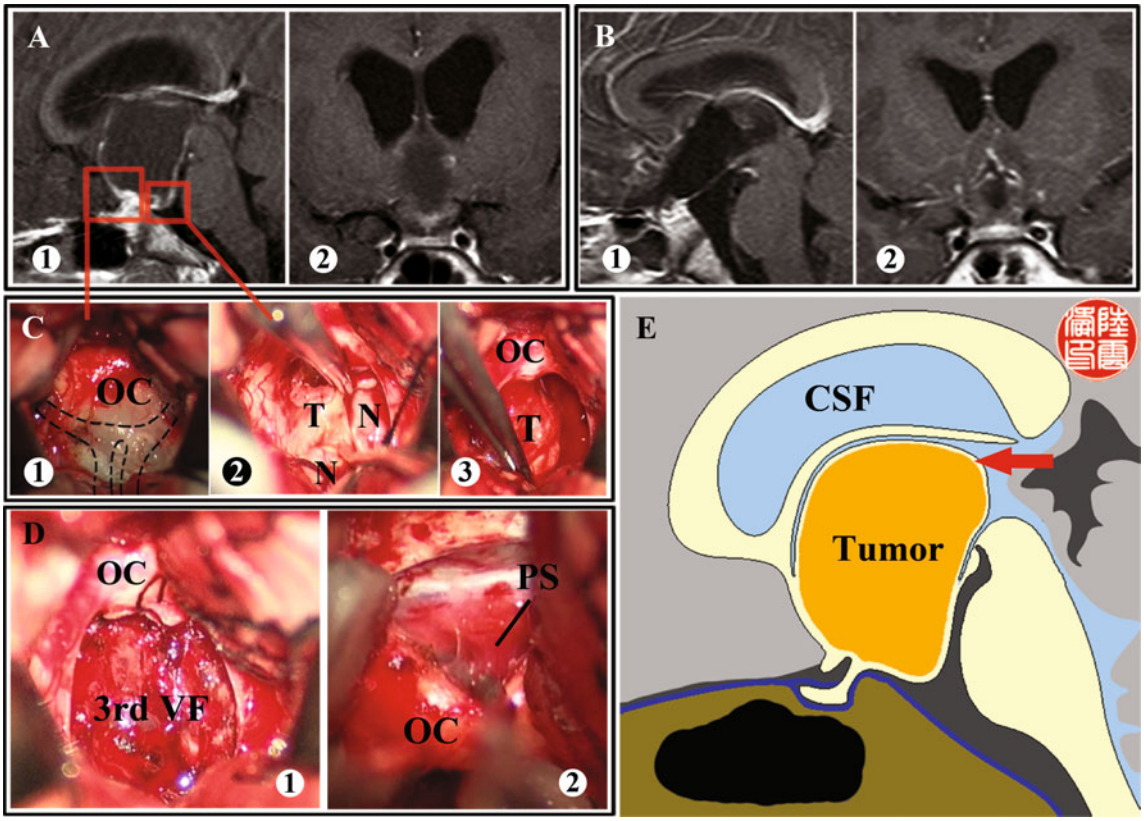

Fig. 2 Showing tumor adherence pattern "b" to the 3rd VF. **a** Presurgical MRI scan (① coronal; ② sagittal). **b** Postsurgical MRI scan (① sagittal; ② coronal). **c** Intrasurgical findings. Exposure of the LT, the tumor was found behind the AcoA, which has been dissected (*dotted lines* show the artery's original location (①)). Well-defined interface between tumor and third ventricular walls can be traced along the tumor capsule though it adherents to the nervous layer widely (②). With tumor separation, the pedicle side of tumor was observed being adherence to the 3rd VF tightly (③). **d** After tumor removal, the integrity of 3rd VF was reserved, while the intactness was impaired because of tumor's wild adherence. And the pituitary stalk was intact, which can be observed through the prechiasmatic space. **e** The schematic diagram of the tumor's growth pattern "b" (*blue area* CSF. Tumors located inside the parenchyma of the ventricular floor with wide basement, which still being covered by a thin nervous layer as indicated by the *red arrow*). *OC* optical chiasm, *T* tumor; *N* nervous layer of the 3rd VF, *PS* pituitary stalk

subtotal tumor removal—STR). Notably, all these four cases with STR demonstrated pattern "c" adherence to 3rd VF.

Postoperative course

Postoperatively, all patients suffered diabetes insipidus and electrolyte disturbance to varying degrees. There was one mortality. This was a 54-year-old man with severe cognitive disturbance and electrolyte disturbances preoperatively. He presented unconscious and underwent emergent external ventricular drainage for acute hydrocephalus. Imaging revealed a predominantly solid tumor located within the third ventricle with several intratumoral cysts on MRI, and a mass of calcification at the tuberoinfundibulum on CT. After hydrocortisone and diuretics, gross total tumor removal was performed utilizing a frontobasal interhemispheric trans-LT approach. Intraoperatively, the tumor was noted to be tightly adherent to the third ventricular walls. During tumor resection, the junction between the ACoA and A2 segment ruptured. This was coagulated to stop bleeding. Postoperatively, the patient experienced derangements of his fluid balance and electrolytes. This necessitated a prolonged stay on the Intensive Care Unit. His conscious level again deteriorated 7 days postoperatively. CT scanning revealed a left-sided ACA infarction. He had a further surgical decompression, but despite medical treatment, he passed away 13 days after the second surgery.

Another case was complicated by a contralateral epidural hematoma due to rapid decrease of intracranial pressure. This also necessitated reoperation. One patient had new onset postoperative psychological symptoms due to frontal lobe contusions. This improved along with regression of brain edema. Sixteen patients underwent resolution of postoperative hypothalamic imbalances following rigorous fluid management. The other complications such as hydrocephalus, cognitive disturbance, and headache underwent similar resolution.

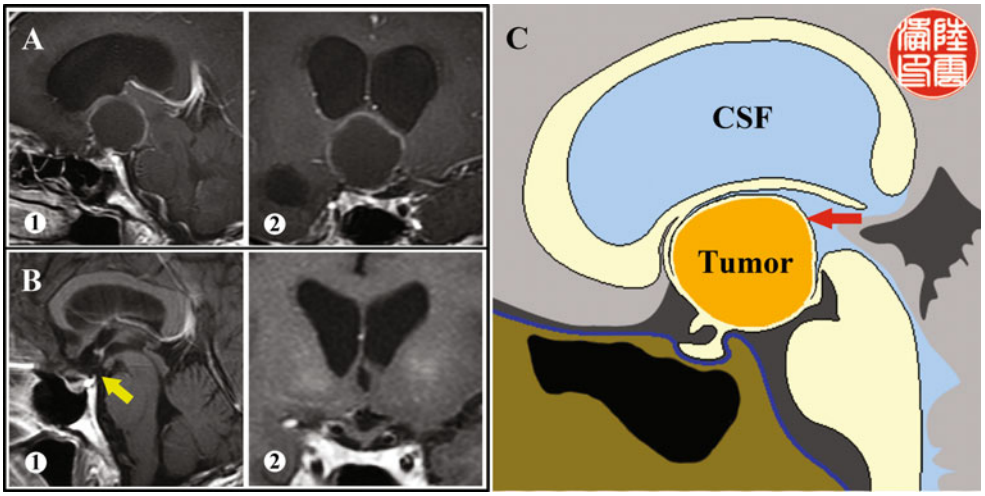

Fig. 3 Showing tumor adherence pattern "c" to the 3rd VF. **a** Presurgical MRI scan (① coronal; ② sagittal). **b** Postsurgical MRI scan (① sagittal; ② coronal). The local defects could be found as the indicated by a *yellow arrowhead*, while the mamillary body was intact. **c** The schematic diagram of the tumor's growth pattern "c" (*blue area* CSF. Although more tight adherence to the 3rd VF, tumors still located inside the parenchyma of the nervous. And an identifiable nervous layer was still found covering the tumors' surface)

Follow-up study

Recurrence rates Of four patients who had STR, three experienced tumor recurrence (at 16, 29, and 62 months, respectively). Not surprisingly, all three cases were closely adhered to the 3rd VF (pattern "c"). None of the patients who underwent total tumor resection had either clinical or radiological evidence of recurrence after a follow-up of 14–117 months (mean 45 months). Reoperation was carried out in the three patients with recurrence. Following surgical management, either stereotactic radiosurgery (gamma knife for two patients) or conventional radiotherapy (in one

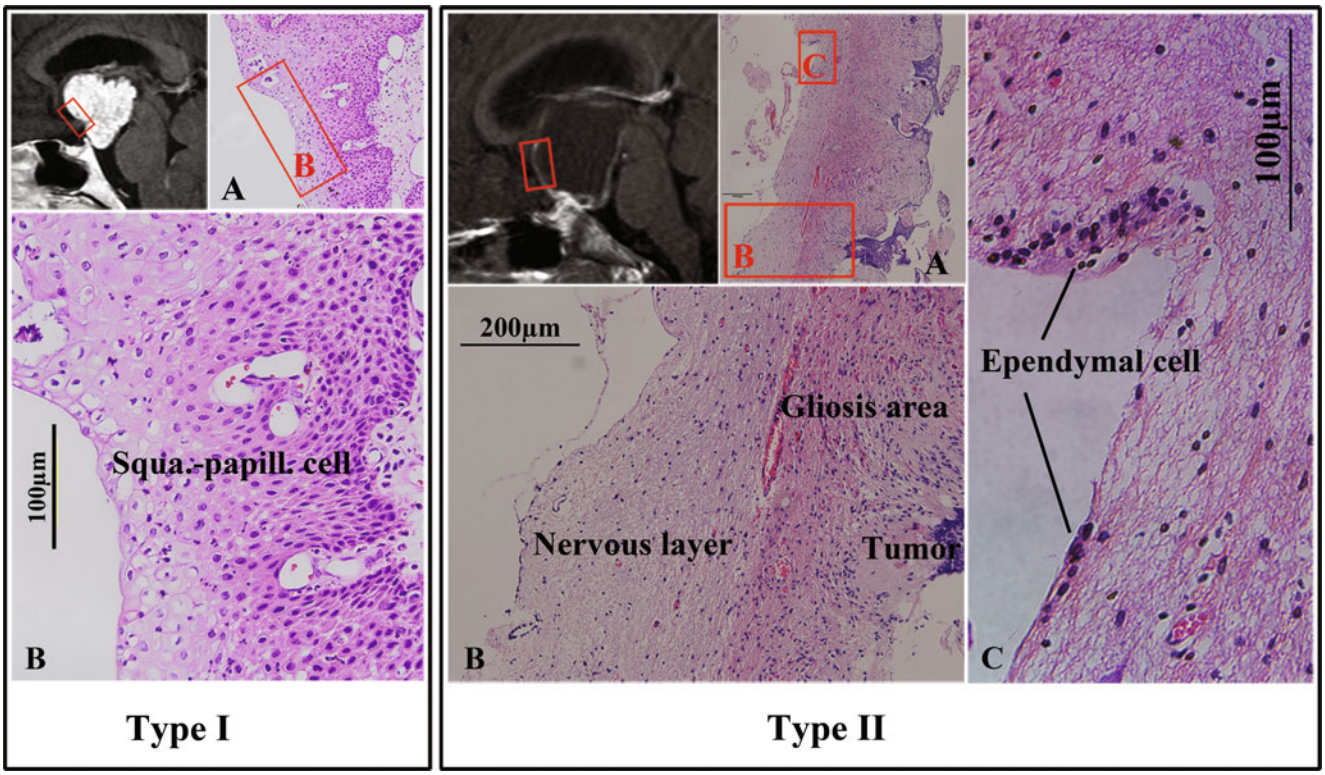

Fig. 4 Showing the stratification of the IVCs. The *red square* in the presurgical MRI showed the location of the tumor specimen (H&E staining). *Type I A* (×40) Macroview of the tumor mass, the *red square area* was magnified as the Figure B; *B* (400×): a smooth outer surface of tumor could be identified with typical stratified squamous epithelium covering. No nervous layer and any ependymal cells could be identified. *Squa.-paplill. cell* squamous-papillary cell. *Type II A* (40×) macroview of the tumor mass, the *red square area* was magnified as the Figure B and C. *Figure B* (×200): a thin nervous layer was observed covering the top of the tumor cystic wall. Furthermore, two different histological layers could be identified in the cystic wall, which was the outer gliosis area and the inner adamant cells layer. *Figure C* (×400): in some regions, several cuboid epithelial cells can be identified covering the outer surface of the nervous layer, which was thought as the ependymal cells

Table 2 Correlation between tumor's adherence pattern, preoperative MRI, and pathology

Adherence pattern	3rd VF on preoperative MRI		Pathology		Total
	Identified	Unidentified	Adamant	Papillary	
Pattern "a"	0	2	0	2	2
Pattern "b"	3	4	4	3	7
Pattern "c"	1	7	7	1	8
Total	4	13	11	6	17

patient) was undertaken. No evidence of further tumor progression was found in two of the three patients. The remaining patient had a further tumor recurrence and ultimately died due to disease progression.

Functional outcome Overall, the functional outcome was deemed "good" in 10 of 17 patients (58.8%), moderate in 3 patients (17.6%), and fair in 2 patients (11.8%). There were two mortalities (11.8%; Table 3). All nine cases with pattern "a" and "b" adherence had favorable outcome (good in eight patients and moderate for one patient). There were eight cases with pattern "c" adherence, and these showed significantly worse outcome than the other two types. These included 25% with moderate outcome (2/8), 25% with fair outcome (2/8), and a 25% mortality rate (2/8). In the two pediatric cases, one suffered postoperative obesity (+3 SD) and tumor recurrence during the follow-up period. Reoperation was carried out on the recurrent tumor. Following reoperation, there was noted to an improvement in the obesity.

Endocrinological outcome Deterioration of anterior pituitary function was observed universally following tumor removal. There was adrenocorticotropic disturbance in four patients, thyrotropic disturbance in five patients, and new-onset panhypopituitarism in three patients. All but one had diabetes insipidus postoperatively. During long-term follow-up, however, only 5 of 16 patients had permanent diabetes insipidus.

Correlation between the degree of adherence to 3rd VF and anterior pituitary function was analyzed. The hypothalamic–pituitary–adrenal (HPA) axis was normal postoperatively in approximately half of the patients with adherence pattern "a" or "b." None of the patients with pattern "c" adherence showed normal adrenal function postoperatively. Postoperative normalization of hypoadrenalism and hypogonadism was observed in one patient each, respectively (with tumor–3rd VF adherence pattern "a" in both cases).

Eleven patients in this series underwent both pre- and postoperative provocation of cortisol, GH, and TSH. Within this group, the adherence pattern of 3rd VF was "a" in two patients, "b" in four patients, and "c" in five patients. Provocation tests of GH secretion were negative postoperatively in all 11 patients, suggesting friability of the pituitary–GH axis. Postoperative cortisol and TSH provocation tests did not elicit any response in patients who had adherence pattern "c." There was normal response in four patients and subnormal response in two patients (of the 6 with adherence pattern "a" and "b"; Table 4).

Table 3 Function outcome of the 17 cases of IVC

Adherence pattern	Functional outcome				Total
	Good	Moderate	Fair	Death	
Pattern "a"	2	0	0	0	2
Pattern "b"	6	1	0	0	7
Pattern "c"	2	2	2	2	8
Total	10	3	2	2	17

Discussion

The definition of IVC

IVC refers to those tumors located exclusively within the third ventricle. Several criteria (such as a patent suprasellar cistern, a normal pituitary stalk, and absence of sellar abnormality on preoperative MR images) have been proposed for the diagnosis of IVC [5, 6, 10]. Despite some initial confusion concerning the topographic relationship between IVC and the 3rd VF, the concept of "pure" or "strict" IVCs emerged in literature. It is currently thought that intactness of the 3rd VF is essential to define a true IVC [4, 16]. Behari et al. described six cases of pure IVC being established on the basis of preoperative MRI revealing an intact 3rd VF. Intraoperatively, three patients with cystic CP were noted to have a well-defined plane of cleavage from the walls of the third ventricle. However, in one case with a cystic lesion and two with solid tumors, a small part of the tumor that was adherent to the 3rd VF could not be removed.

Notably, Pascual [16] in 2004 summarized two different topographic entities as strictly or nonstrictly IVC following

Table 4 Pre- and postoperative incidence of normal anterior pituitary function of the 11 IVCs

Normal anterior pituitary function		Adherence pattern		
		Pattern "a" (2 cases)	Pattern "b" (4 cases)	Pattern "c" (5 cases)
Hypo-pit-adrenal axis	Pre-op	1	3	3
	Post-op	2	2	0
Hypo-pit-GH axis	Pre-op	1	2	2
	Post-op	0	0	0
Hypo-pit-thyroid axis	Pre-op	1	3	2
	Post-op	1	1	0

an extensive review of well-described cases of CPs with an intraventricular location. This has contributed much to understanding of the IVC. In the article, three criteria were used to identify a "strict" IVC. This was an identifiably intact 3rd VF pre-, intra-, and postoperatively. In 2008, schematic drawings [22] were provided illustrating the different stratification of the strict and nonstrict IVC in detail. The theoretical topographical relationships between the tumor and the 3rd VF were described as:

(1) suprasellar tumor pushing the intact third ventricle floor upward (pseudointraventricular CP),
(2) suprasellar mass invading through the 3rd VF and entering the third ventricle cavity (secondarily intraventricular CP),
(3) intraventricular mass within the third ventricle cavity and floor, the latter being replaced by tumor (nonstrictly IVC), and
(4) intraventricular mass completely located within the third ventricle cavity with the intact floor lying below its inferior surface (strictly IVC).

In the current study, all 17 cases were proved by both preoperative MR and intraoperative observation to consist of tumors entirely located within the third ventricular cavity. These were associated with a patent suprasellar cistern and an intact pituitary stalk, and no tumor extension was found inside the subarachnoid cistern. Hence, these 17 cases of IVCs were considered to be truly intraventricular, and not pseudo- or secondarily intraventricular CP. Although three types of adherence pattern of tumor to the 3rd VF were observed in this study, all IVCs were attached tightly to the neural tissue layer at the site of the tuber cinereum and/or the infundibulum. With total tumor removal, it was impossible to preserve a totally intact ventricular floor even with the pattern "a" tumors (two cases), which only have a pedicle stem to attach to the 3rd VF. Notably, following histological analysis of the two cases with pattern "a" adherence, it was found that tumor protruded into the ventricular cavity without an identifiable neural tissue-covering layer (Fig. 5a). This is most likely with the "purely" or "strictly" intraventricular tumors. A clear separation between tumor and ventricular walls can be identified intraoperatively. However, the main components of the 3rd VF, the infundibulum and tuber cinereum, are in close adherence with the pedicle stem of these tumors, thus negating preservation of the 3rd VF following total tumor resection. Additionally, the 3rd VF could not be identified in both cases on preoperative imaging. But postoperatively, adequate thickness was noted in both cases indicating preservation.

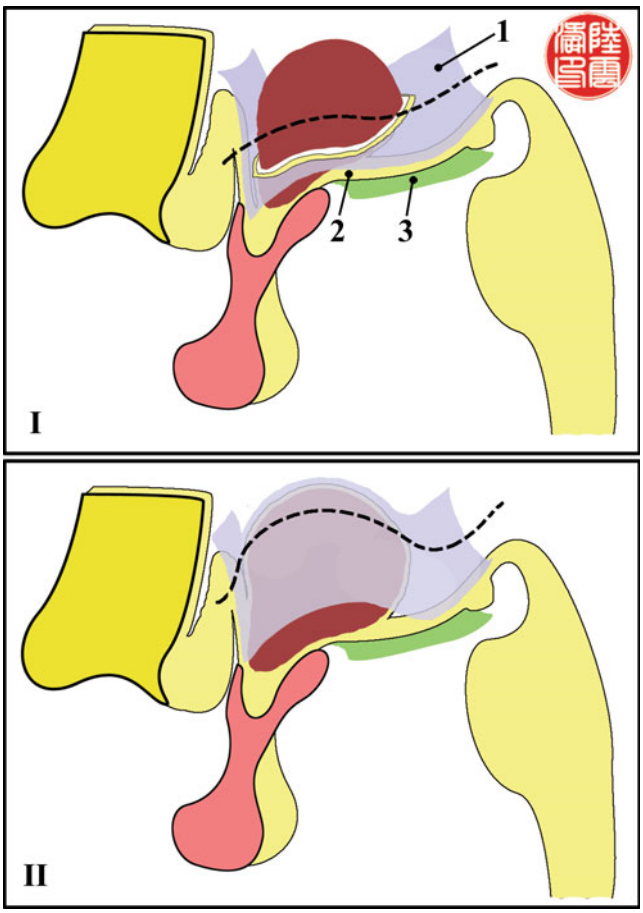

Fig. 5 The stratification of the IVC. **a** Tumor protruded into the third ventricular cavity, without ependymal cellular layer (*1*) and nervous layer (*2*) covering. **b** Tumor located inside the ventricular floor, with ependymal cellular layer and nervous layer covering the surface of the tumor. Both two types of tumor located inside the pia mater layer (*3*)

In the remaining 15 cases, intraoperative inspection and histological stratification showed an identifiable neural layer and an ependymal layer covering the tumor surface. This implies that tumor located within the floor causes inflammation of neural tissue and upward displacement of the ependymal layer (Fig. 5b). It was difficult to free tumor from the tuberoinfundibulum due to tumor adherence in all 15 cases. However, 7 of these 15 cases had a relatively well-defined plane of cleavage from the ventricular wall (pattern "b"), while the other 8 cases (pattern "c") did not. Preservation of the 3rd VF was better with the former than latter, although most of the cases had a membranous attenuated floor. Among the eight cases with pattern "c," there was a local defect following total resection in four cases. Interestingly, among the four cases with an identifiable 3rd VF on preoperative MRI, one pattern "c" case resulted in a local defect following tumor removal.

In summary, several conclusions can be drawn: (1) Preoperative MRI was not correlated to the tumor–3rd VF relationship directly. Identification of 3rd VF on preoperative MRI does not necessarily indicate a purely intraventricular tumor; (2) Intraventricular tumors—even the tumors classed as "strictly IVC," located purely within the cavity without ependymal or neural tissue covering—still have a pedicle stem in close attachment to the 3rd VF. Following total tumor removal, the ependymal and neural layer cannot be totally preserved. In some "nonstrictly" cases, the 3rd VF can be preserved without local defect. Only the anatomical stratifications observed intraoperatively and confirmed histologically were the basis for distinction of "strictly" versus "nonstrictly" IVC (rather than the inspection of 3rd VF pre-, intra-, or postoperatively for preservation); (3) With regard to the tumor stratification, in keeping with the embryonic theory of the origin of CPs, IVCs develop from the epithelial cell rests (remnants of Rathke's pouch) and are found within the neuroectoderm of the developing cerebral vesicle. This occurs when the pars tuberalis comes into contact with the diencephalic infundibular evagination, before the pia mater covers the basal brain surface [23]. Our study showed that, with progressive growth, some tumors will attenuate and finally break through the ependymal layer and simulate a so-called intrinsic IVC, while others may fill up the cavity of third ventricle chamber but still be embedded within the thinning neural tissue layer of the 3rd VF. In our opinion, the terms "strictly" or "nonstrictly" IVC do not indicate the true growth pattern of CPs located exclusively within the third ventricle cavity, as depicted in previous reports [16, 22]. All IVCs, be they "strictly" or "nonstrictly" cases, had a similar site of origin, and the variation observed was the result of differential growth and variable patterns of invasion into surrounding structures.

We also analyzed the relationship between subtypes of CP with an intraventricular location. The results showed that both the adamantinomatous and papillary subtypes of CP can be intraventricular. This finding is replicated in previous reports [16, 24]. The adamantinomatous subtype comprised 73.3% (11/15) of tumors demonstrating pattern "b" and "c" adherence. However, there were no pattern "a" tumors. This also indicates that adamantinomatous CPs tended to adhere more closely to neural tissue than the squamous-papillary one. Further study into the genesis of these histological variants would be of benefit.

Surgical removal of IVC

Surgical resection of IVCs presents specific problems due to deep localization and risk of damage to the optic pathways and hypothalamic structures. The trans-LT route is commonly used in resection of IVCs [6, 24–30]. It offers a more direct access to the anterior part of the third ventricle where the tumor lies adherent in the region of the tuber cinereum. The LT is accessible either along the medial part of a frontotemporal approach or via a anterior interhemispheric approach [19, 24, 31–37]. When a lateral approach is used to access the LT, the oblique angle at which the LT is viewed makes it difficult to see the posterior part of the third ventricle and hence, contributes to difficulty in opening the entire LT. Tumors with wide and tight adherence to the third ventricle wall and/or floor cannot be safely dissected through the lateral approach as there is a lack of direct vision of the posterior part of the third ventricle. The anterior interhemispheric approach, on the other hand, provides a good view of the entire LT. Tumors can be removed either through the space anterior to the AcoA, or more often, through the bilateral A_2 space, in cases where the AcoA is located close to the optic chiasm. The ACoA can be safely divided in some cases when it limits operative exposure [34, 35]. Tracing the tumor boundary through a relatively narrow space such as the LT sometimes leads to extreme difficulties. Internal decompression by aspirating cystic components or piecemeal extirpation of solid parts of the tumor can help in gaining space to facilitate dissection of the tumor from the third ventricle margins.

Anatomic maintenance of the ventricular floor and walls and of the infundibulum is of paramount important during tumor removal. The irregular adherence pattern between the tumor, 3rd VF, and walls demands special attention. It guides the surgeon's decision as to the extent of tumoral resection that can be performed and predicts the feasibility of preservation of the 3rd VF and hypothalamic structures [16]. A precise inspection of the superior aspect of the tumor surface is required immediately after the opening of LT to clarify whether or not the tumor has a layer of nerve

tissue. One should always remember that except for the few tumors with growth pattern "a," for the majority of cases, the capsule of the tumor was dissected and delivered from the surrounding layer of gliosis. This neuroglial layer intervening between the tumor and viable hypothalamic nuclei may provide a safe dissecting plane [38], through which a total removal of the lesion may be carried out in most cases. However, there are dense adhesions in some cases, thereby rendering it impossible for the surgeon to follow a clear plane of cleavage without causing significant damage to viable neural tissue. In such situations, a radical resection cannot be completed.

As mentioned above, preservation of the 3rd VF was impossible as all the tumors have at least some attenuation at the site of the tuber cinereum. In this cohort, four cases with growth pattern "c" resulted in a small local defect at the anterior part of the third VF following total tumor removal. In the remaining 13 cases, the integrality of the 3rd VF was preserved, though some residual tumor was left in situ where there was tight adherence.

The resectability and recurrence of IVCs following GTR have not been adequately studied due to their relative rarity. Existing case series are small in number as a result. We achieved 76.4% (13/17) of our cases and underwent GTR with one postoperative death. Of note, there has been no recurrence in those patients in our study whose IVCs were totally resected. This indicates the potential significance of radical resection on reducing tumor recurrence. Therefore, we propose that radical resection including removal of gliotic tissue with tumor invasion should be attempted as a first-line therapeutic strategy.

Prognosis of IVC

IVCs demonstrate slow progressive growth that can be fatal due to eventual compression of the hypothalamic structures and hydrocephalus. Therefore, local control is the primary goal of therapy. Management of CPs remains controversial due to divided opinions on the extent of tumor removal and the prognosis. Commonly, the tumor–3rd VF relationship is the main determinant of the surgical strategy. In this cohort, following functional evaluation, 12 of 13 cases with total tumor removal had a "Good" (9/13, 69.2%) or "Moderate" (3/13, 23.1%) outcome, and none of these had tumor recurrence during follow-up. On the other hand, three cases of pattern "c" IVC with tight adherence to the ventricular floor necessitating STR inevitably demonstrated tumor recurrence. Reoperation and adjunctive radiotherapy were carried out for these. One suffered further tumor recurrence and ultimately died of uncontrolled disease. Although no evidence of tumor progression was found in the other two cases, the conclusion of "Fair" outcome reflected the lower quality of life these patients subsequently had.

A significantly improved outcome was observed in patients who had tumor growth pattern "a" and "b," as well as those patients in whom no residual tumor was noted on postoperative MRI. This indicates that the degree of tumor adherence to the 3rd VF may have a prognostic value on both tumor resectability and stability during follow-up.

Another important marker of prognosis is the presence of endocrinological disturbance as a common iatrogenic complication of treatment of CPs. Diabetes insipidus, frequently associated with suprasellar CPs, was infrequently reported with IVCs despite the proximity of the lesion to the HPA. As this study showed, in spite of all patients suffering diabetes insipidus and electrolyte disturbance during the immediate postoperative course, only 5 (31%) actually developed permanent diabetes insipidus during follow-up. These results are significantly better when compared to those for suprasellar CPs. One explanation is that the pituitary stalk is more amenable to preservation in IVCs than suprasellar CPs. This is due to the high position of the tumor.

Dysfunction of the HPA axis can be due to either the tumor itself or to the treatment [39, 40]. HPA dysfunction usually occurs following surgical management of these tumors. Maira et al. reported five cases of postoperative panhypopituitarism in their eight intraventricular cases [24]. We observed generalized deterioration of anterior pituitary function postoperatively, with three cases of new-onset panhypopituitarism. In keeping with the literature [40, 41], the most common abnormality noted was somatotrophic axis deficiency (all patients) and gonadotrophic axis deficiency (92.9%). Although anatomical preservation of the 3rd VF does not necessarily correlate with preservation of function, our results indicate that tumors less adherent to the 3rd VF (being pattern "a" and "b") showed better outcome with regard to adrenocorticotropic and thyrotrophic axis function than tumors with growth pattern "c."

In children, obesity was another important means of evaluation of prognosis. Lee et al. [42] comparatively analyzed the HPA axis dysfunction of 27 cases of intrasellar CPs and 39 cases of third ventricular CPs. Their results were that children with sellar tumors had a greater incidence of pituitary hormone disturbance, while those with third ventricle tumors had a greater prevalence of obesity. There is no indication within the literature of the incidence of IVC in children. In our study, only two pediatric cases of IVC were identified among a total of 195 cases (81 children) of CPs. One of them suffered obesity and tumor recurrence after initial surgery. However, the obesity gradually resolved following reoperation. As the third ventricular cases in Lee's series included tumors involving the suprasellar region (which can be thought of as intra- and extraventricular type of Steno [29] or the

secondary third ventricular tumor of Pascual [16]), the outcome of childhood IVCs remains to be established.

Conclusion

IVCs show some unique clinical and pathological features in comparison to suprasellar tumors. There is however significant variation within IVCs alone—such as the adherence patterns to the 3rd VF and the tumor's stratifications. In this cohort, the adherence pattern was classified as:

(a) pedicle attachment,
(b) wide attachment but dissectible tumor boundary, and
(c) wide tight attachment.

Additionally, with histological analysis, two kinds of tumor stratification were found in IVC:

(1) tumor invading the third ventricular cavity without a nerve tissue layer
(2) tumor covered by a thin nerve tissue layer and intermittent ependymal cells.

The consideration of IVCs as "strictly" or "nonstrictly" IVC may not be able to indicate true tumor growth. With high possibility, all IVCs including "strictly" or "nonstrictly" cases had a uniform site of origin. This site of origin is in close relation to the infundibulum and the tuber cinereum. The variables noted were the results of different growth patterns and patterns of invasion. The adherence pattern and tumor stratification were correlated with the extent of tumor removal and prognosis. A better understanding of these morphological features of IVCs might improve the surgical treatment of tumor type.

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