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Original Article

Radical Resection of Craniopharyngioma: Discussions Based on Long-term Clinical Course and Histopathology of the Dissection Plane

Tomu Okada, Kazuhiko Fujitsu, Teruo Ichikawa, Kousuke Miyahara, Shin Tanino, Yasuhiro Uriu, Yuusuke Tanaka, Hitosi Niino[1], Saburou Yagishita[1]

Departments of Neurosurgery and [1]Pathology, National Hospital Organization, Yokohama Medical Center, Yokohama, Japan

Abstract

Objective: Craniopharyngioma is a benign tumor. However, sometimes, this tumor may recur repeatedly even after apparent total resection. This study investigated the requirements for ideal radical treatment, based on a discussion of the long-term clinical course and pathological findings in surgical patients. **Methods:** We performed 81 surgical procedures for 67 patients with craniopharyngioma between February 1990 and December 2015. We classified patients into Groups I–III according to emphasis of surgery in chronological order, so we investigated the tumor recurrence rate and the necessity for postoperative hormonal replacement. **Results:** Multiple comparison of results from the three groups found significant differences in recurrence rate between Groups I and II (P = 0.0111) and Groups I and III (P = 0.0056). Although there were no differences in recurrence rate between Groups II and III, mortality rate of Group III was lower than that of Group II. No significant difference was seen between any group in terms of hormonal replacement. **Conclusions:** These results strongly suggest that the radical resection used to treat patients in Group III should be given priority as the procedure for removing craniopharyngioma.

Keywords: *Craniopharyngioma, dissection plane, hormone replacement therapy, ideal total resection, radical resection*

Introduction

Craniopharyngioma is thought to originate from remnants of the craniopharyngeal duct, and that is a benign tumor to be locate from intra turucica to suprasellar region.[1,2]

There are many reports up to now that total removal of the tumor represents the most effective method of radical treatment,[2-14] but morbidity and mortality associated with total resection are not necessarily low.[12] Postoperative treatments including stereotactic radiotherapy after partial resection are carried out so as not to cause postoperative deterioration; however, many patients experience repeated regrowth or recurrence and gradually lose their daily activities.[8,9,15,16] We have so far performed craniotomy 81 times on 67 patients, but some patients have experienced tumor recurrence even after obvious complete resection. This study investigated the requirements for ideal radical treatment, in the light of a discussion of the long-term clinical course and pathological findings in surgical patients.

Methods

We performed craniotomy 81 times on 67 patients (27 males, 40 females; 50 adults ≥20 years old; 17 minors <20 years old; mean age, 40.6 years; range 1–75 years) between February 1990 and December 2015. Mean duration of follow-up was 146.3 months (range, 12–310 months). The surgical approach was a basal interhemispheric approach (bIHA)[17] or an expanded and improved version of this approach (combined supra- and infra-chiasmatic approach[18] or median splitting[19]) in 54 cases, an orbitozygomatic approach (OZA) or an expanded and improved version of this approach (transtemporal transchoroidal fissure approach[20,21]) in 25, and pterional approach in 2. The histopathological diagnosis was adamantinomatous type in 34 cases, squamous-papillary type in 30, mixed type[22] in 2, and ciliated type[23] in 1.

Recurrence was defined as the point at which a tumor was clearly visible on imaging during postoperative follow-up. Mean time to recurrence was 29.2 months (range 5–78 months). The proportion of patients in which recurrence was identified was taken

Address for correspondence:
Dr. Tomu Okada, Department of Neurosurgery, National Hospital Organization, Yokohama Medical Center, Yokohama, Japan.
E-mail: tomuokada-nsu@umin.ac.jp

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as the recurrence rate. The need for hormonal replacement was defined as continuous administration up to the present day of one or more of adrenocortical hormone, thyroid hormone, growth hormone, and antidiuretic hormone. The proportion of patients receiving such treatment was taken as the hormonal replacement rate. Ideal total resection was defined as successful total resection that preserved the pituitary stalk both anatomically and functionally, with no evident recurrence to date, and the proportion of patients in whom this was achieved was taken as the ideal total resection rate. We categorized patients into the following three groups for analysis.

Group I: Twenty-four patients who underwent total removal of the tumor with the aim of anatomical preservation of the pituitary stalk (mainly 1990–2000).

Group II: Twenty-six patients in whom total removal of the tumor was attempted, including resection of the pituitary stalk and part or all the pituitary if preservation of pituitary function was judged as infeasible, but with an effort made to preserve the hypothalamus. This group is a transitional period from Group I to Group III (mainly 2001–2008).

Group III: Seventeen patients in whom priority was given to total removal of the tumor that emphasized radical surface dissection as described below (2009–2015) [Table 1].

The procedure used for patients in Group III requires some explanation. If tumor invasion was evident as far as hypothalamus, the tumor was resected with a focus on the pathology of the dissection surface, even if this entailed perforating the floor of the third ventricle [Figure 1a-d]. Observation of the histopathology of our patients revealed that if a tumor had infiltrated the junction between the hypothalamus and pituitary stalk, tumor tissue was scattered within the glial layer, which was rich in Rosenthal fibers [Figure 2a]. Although scattered tumor tissue was also present in the tumor capsule where it adhered to the lateral wall of the third ventricle, this was not seen on the other side of the capsule [Figure 2b]. Therefore, we thought that it was the total resection method with emphasis on curative radical plane that we removed the tumor until a perforation up to 10 mm in diameter communicating with the interpeduncular cistern was created in the floor of the third ventricle, including the semitransparent viscous capsule (glial layer) [Figure 3a and b], and until petechiae appeared on the lateral wall of the third ventricle corresponding to the lateral surface of the hypothalamus, when there were areas of firm adhesions to the inferior surface of the hypothalamus or where there was obvious infiltration of this area [Figure 3c and d].

A retrospective analysis for the surgery and outcome was performed using SPSS Statistics version 22.0 (SPSS Inc, IBM, USA) software. Bonferroni's method was used for multiple comparisons between the three groups, and $P < 0.05/3 = 0.0166$ was regarded statistically significant. This article showed a result operated on based on the discretion of the surgeon, and we did not obtain consent of

Table 1: Clinical profile of patients (*n* =81)

Gender	
Male	27
Female	40
Age at surgery (years)	40.6 (1-75 years)
Follow-up (months)	146.3 (12-31 months)
Surgical approach	
Basal interhemispheric approach	54
Orbitozygomatic approach	25
Pterional approach	2
Surgical procedure	
Group I	24
Group II	26
Group III	17
Histopathological diagnosis	
Adamantinomatous	34
Squamous-papillary	30
Mixed	2
Ciliated	1

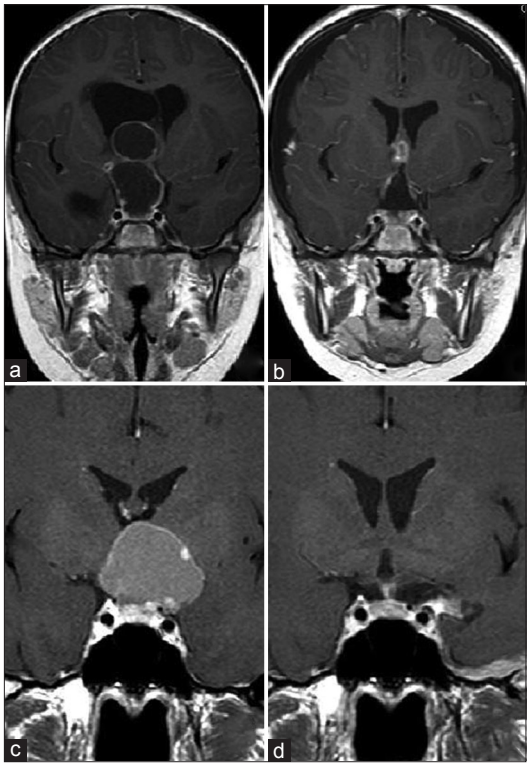

Figure 1: Pre- and post-operative magnetic resonance image in Group III. (a) This picture obtained in a 3-year-old boy. Preoperative coronal-enhanced magnetic resonance image shows a multicystic craniopharyngioma extending into the entire third ventricle. (b) Postoperative (basal interhemispheric approach) coronal-enhanced magnetic resonance image shows total removal of the tumor. (c) This picture obtained in a 38-year-old man. Preoperative coronal-enhanced magnetic resonance image shows a solid craniopharyngioma that slightly protrudes to the left side. (d) Postoperative (transchoroidal fissure approach) coronal-enhanced magnetic resonance image shows total removal of the tumor

the patients to be enrolled other than preoperative written consent.

Results

In Group I (n = 24), the recurrence rate was 45.8% (11/24), the hormonal replacement rate was 87.5% (21/24), the ideal total resection rate was 12.5% (3/24), and the mortality rate was 0% (0/24).

In Group II (n = 26), the recurrence rate was 12.5% (3/26), the hormonal replacement rate was 79.1% (19/26), the ideal total resection rate was 20.8% (5/26), and the mortality rate was 7.7% (2/26).

In Group III (n = 17), the recurrence rate was 5.9% (1/17), the hormonal replacement rate was 88.2% (15/17), the ideal total resection rate was 11.7% (2/17), and the mortality rate was 0% (0/17).

Multiple comparison of results from the three groups [Table 2] found significant differences in recurrence rate between Groups I and II (P = 0.0111) and Groups I and III (P = 0.0056), but not between Groups II and III. No significant difference was seen between any group in terms of hormonal replacement rate, ideal total resection rate, or mortality rate [Figure 4a-d].

Recurrence was not seen in any of the patients who did not require hormonal replacement (3 in Group I, 5 in Group II, and 2 in Group III). Of the 10 patients in whom ideal total resection was achieved, the 8 patients in Groups I and II all showed distal-type tumors, with the site of origin of the tumor being distal to the point at which the hypothalamus attached to the pituitary stalk. Both patients in Group III showed proximal-type tumors, with the site of origin in the hypothalamus-pituitary stalk junction. All patients for whom ideal total resection could not be performed in all three groups displayed either total-type tumors in which the site of origin could not be determined, intra-stalk-type tumors with the site of origin within the pituitary stalk, or with the site of origin around the site of adhesion of the pituitary stalk to the hypothalamus and widespread, tight adhesions between the tumor and normal tissue. In Group III, the group for which detailed information is most important, all 17 tumors were either proximal or total-type, with no patients showing distal-type tumor. Perforation of the hypothalamus-pituitary stalk junction occurred in all cases to various extents. Both patients in whom ideal total resection was achieved suffered perforations of around a few millimeters in this region; however, in both cases, the anatomical continuity of this region was preserved, with no damage to the perforators. In both cases, hormonal replacement was temporarily required, but both patients (2 adults) were subsequently weaned off this treatment (after 1 month and 3 months).

Figure 5a-d shows intraoperative findings from one of these patients.

As Gamma knife surgery on the retrochiasm has also been reported as effective,[24] this method was performed for three patients (2 in Group I, 1 in Group II) with tumors that had recurred in this area, but all three subsequently experienced further recurrence.

Table 2: Rates of recurrence, hormonal replacement, ideal total resection, and mortality in relation to case groupings

Group	I (n=24)	II (n=26,†2)	III (n=17)
Recurrence	11 (45.8%)	3 (12.5%)	1 (5.9%)
Hormonal replacement	21 (87.5%)	19 (79.1%)	15 (88.2%)
Ideal total resection	3 (12.5%)	5 (20.8%)	2 (11.7%)
Mortality	0 (0%)	2 (7.7%)	0 (0%)

n – number of patients; † – deaths

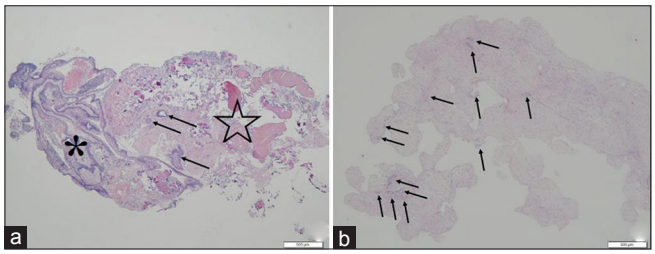

Figure 2: Pathological findings (hematoxylin and eosin stain) of surgical specimen obtained from a patient with suprasellar craniopharyngioma. (a) Tumor tissues (*) are scattered (arrows) in the hypothalamic glial layer. Numerous Rosenthal fibers (☆) are also apparent. (b) Histopathology of the semitranslucent glial layer attached to the ependymal layer of the third ventricle. No tumor cells are detected in this layer except that normal ependymal cells are occasionally observed (arrows)

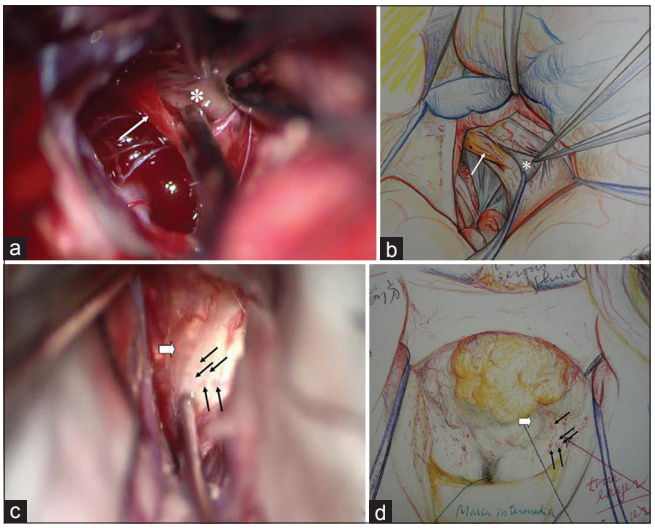

Figure 3: Intraoperative photographs and illustrations from operative notes. (a and b) A perforation (*) of the third ventricular floor behind the pituitary stalk (arrow) in a case of suprasellar craniopharyngioma. Operation was performed using the transchoroidal fissure approach. (c and d) Removal of third ventricular craniopharyngioma. Surgery was performed through the basal interhemispheric approach. Arrows show multiple petechiae after dissection of the semitranslucent glial layer covering the tumor (box arrow)

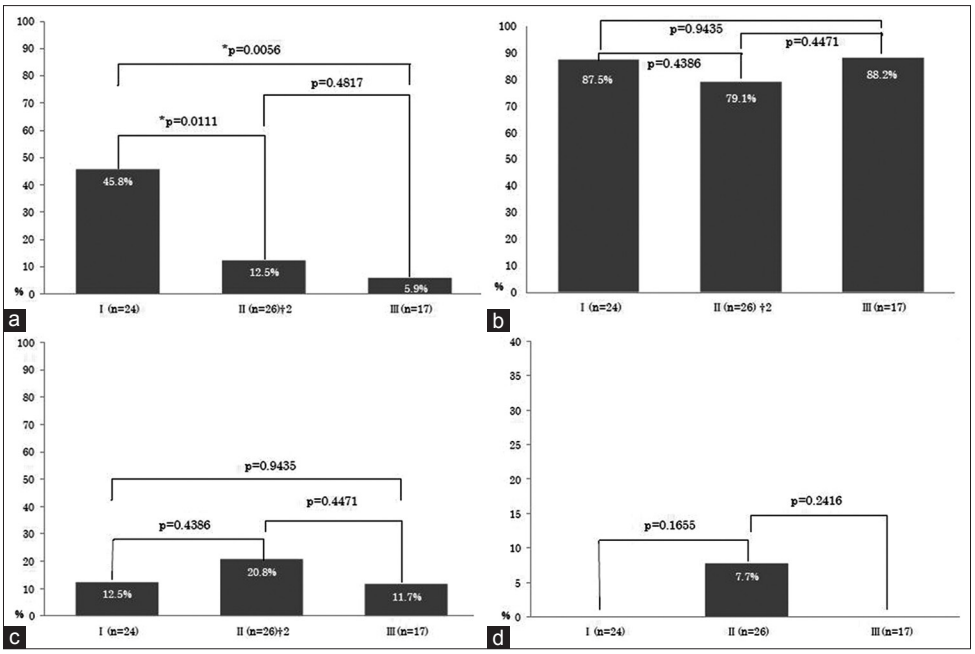

Figure 4: Multiple comparison corrections with Bonferroni method. **P* < 0.0166; †deaths. (a) Recurrence rate. (b) Rate of hormone replacement. (c) Ideal total resection rate. (d) Mortality rate

Finally, although not all patients underwent an objective assessment of cognitive function, all patients in Groups I–III in whom recurrence had not occurred by the final follow-up are continuing to lead daily lives of equivalent or better quality compared with before surgery (Karnofsky performance status ≥80%).

Discussion

Change from Group I to Group II

Although no significant difference was seen between Groups I and II in either the need for hormonal replacement or the rate of ideal total resection, the recurrence rate was significantly lower in Group II compared with Group I. This was an endorsement of the policy used for patients in Group II, whereby if the pituitary stalk could not be anatomically preserved only as fine palisades or semitransparent membranous tissue, then functional preservation was regarded as infeasible and the focus was shifted to resection of the entire tumor. Focusing on preservation of the pituitary stalk and leaving residual fragments of tumor might be thought to increase the risk of recurrence. The tiny fragments of tumor tissue, however, are not limited to the pituitary and pituitary stalk. In many cases, the tumor is also present in the area where the pituitary stalk attaches to the hypothalamus, that is, within the hypothalamus itself, mainly in the median eminence. Thorough going total resection of the tumor frequently entails deliberate perforation of the floor of the third ventricle. On this basis, we gradually changed our procedure to the type of resection carried out for patients in Group III. Two patients in Group II died, and in both cases, the cause of death was electrolyte balance volatility due to

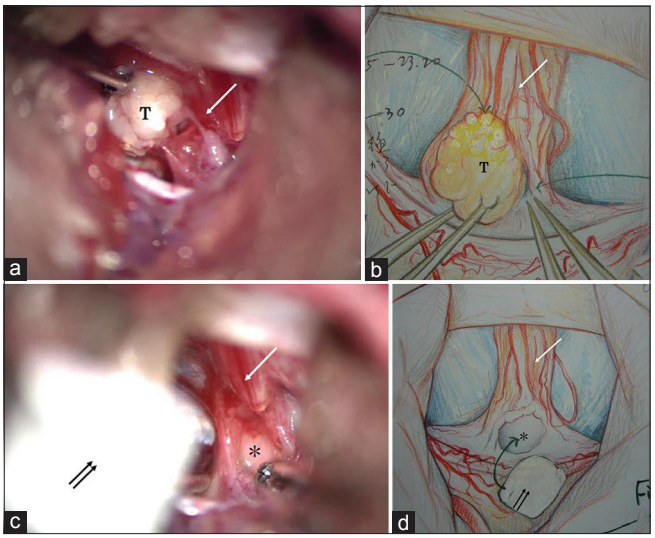

Figure 5: Intraoperative photograph and illustrations from operative notes in a Group III case with ideal total resection. Surgery was performed using a basal interhemispheric approach. (a and b) Removal of the last piece of tumor. T, tumor; arrow, pituitary stalk. (c and d) A 5- to 7-mm square perforation in the floor of the third ventricle (*). Double arrows, gelform covering the perforation

postoperative adipsia.[25] These clinical courses represented not only a problem of postoperative management but also dysfunction of the thirst center that may have been damaged by inappropriate dissection in the hypothalamus as a result of inexperience.

Shift from Group II to Group III

In the light of this experience, since 2009, we have been carrying out removal of the tumor with a focus on radical surface dissection, with the expectation that this will reduce

both the recurrence rate and the rate of adverse events, on the basis of the pathological investigation described above. In terms of approach, mostly for very large tumors with suprasellar development that extends past the foramen of Monro into the third ventricle [Figure 1a and b] we use a combined supra- and infra-chiasmatic approach. Namely, in addition to bIHA, the crista galli was removed, the anterior communicating artery or unilateral anterior cerebral artery (A1) was cut, and the lamina terminalis was opened.[17-19] Meanwhile for mainly suprasellar tumors or tumors with lateral deviation [Figure 1c and d], we use transtemporal transchoroidal fissure approach. Namely, in addition to OZA, the choroidal fissure in the temporal horn was opened and we performed with manipulation behind the optic chiasm from posteriorly manipulation, and manipulation within the sella from anteriorly while looking downward.[6,18,20,21] Whichever approach is used, we begin with operations on the inferior surface of the chiasm to preserve pituitary function. If the tumor is of the distal type, ideal total resection is more likely to be feasible; however, if preservation of the pituitary stalk is judged as impossible, then priority is given to total resection of the tumor. As we can be seen from our experience with 2 cases in Group III, however, ideal resection of proximal-type tumors is achievable on condition that there is no widespread tumor infiltration of the hypothalamus-pituitary stalk junction and the tissue in this area can be anatomically preserved microscopically, even if perforation of this site does occur. Our procedure was to perform careful internal decompression and then try not to leave any fragment of tumor tissue, being careful to remove the dissection plane of the tumor as *en bloc* as far as possible, and if any fragment was scattered, we carried out immediate pathological diagnosis for each one to confirm whether tumor tissue was present. This procedure reduced the recurrence rate for patients in Group III to 5.9% (1/17), significantly lower than that of Group I, by focusing carefully on the site of attachment to the wall of the third ventricle and areas of invasion in the hypothalamus and resecting the dissection plane, which was regarded as pathologically curative. Although no significant difference from Group II was apparent, this represented the lowest recurrence rate seen in any of the three groups. No patient in this group died (mean follow-up for Group III, 43.4 months; range, 12-80 months). The only case of recurrence in Group III was a proximal-type tumor, but this was regarded as a drop metastasis of the tumor in the surgical approach route (bIHA) and not localized recurrence close to the site of origin.

However, the hormonal replacement rate was 88.2% (15/17) and the ideal total resection rate was 11.7% (2/17), not significantly different from those of the other two groups. Given that Groups I and II included several patients with distal-type tumors, which offer a greater chance of ideal total resection, whereas not a single distal-type tumor was seen among patients in Group III, a careful focus on radical resection may be incompatible with the preservation of endocrine function as a target. Of course, the differences over time in the results for Groups I–III may also reflect the development and improvement of surgical techniques and the acquisition of surgical skill itself.

Moreover, as the follow-up period of Group III is shorter than the others, the recurrence rate of Group III may occur lower possibly. However, two-third of all recurrent cases (10/15), especially three-quarters of recurrent cases in Group II–III (3/4), were recurrent within 12 months (7 in Group I, 2 in Group II, 1 in Group III). Therefore, we considered that we could not disregard the low recurrence rate of Group III which follow-up period is at least more than 12 months. In any case, we have to follow-up these cases more carefully in the future.

Debate concerning the tumor dissection surface and histological/anatomical discussion of the hypothalamus

Conventionally, for large tumors that have grown into the third ventricle, emphasis is placed on taking care not to damage either the hypothalamus or the lateral wall of the third ventricle during resection,[5,9] but there has been no detailed description of how far resection can actually be taken.

Kempe warned that resecting as far as the glial layer that lies between the tumor and normal brain tissue will damage the hypothalamus and may potentially prove fatal,[26] but conversely Sweet stated that dissecting the glial layer is not only safe but also enables radical resection,[10] and Weiner *et al*. also supported this theory.[12]

In our own surgical experience, for areas that are only touching the lateral wall of the third ventricle, complete dissection without losing sight of the capsule is sufficient, but for areas that adhere tightly to the hypothalamus or where invasion is severe, resection that focuses pathologically on the dissected surface is the sort of dissection that will improve the curative rate. Samples of normal brain tissue with no brain disease or trauma obtained from autopsy patients did not contain any neuronal nuclei on the side of the median eminence corresponding to the inferior surface of the hypothalamus. However, on the surface of the wall of the third ventricle corresponding to the lateral surface of the hypothalamus, there was a gap of approximately 200–500 μm between the ependymal tissue and the nearest paraventricular nuclei [Figure 6], and distances to other hypothalamic nuclei were even greater. For tumors that had grown deep into the suprasellar region, the hypothalamus had turned almost entirely into membranous tissue, and the hypothalamic nuclei were displaced to both sides. Neuronal nuclei were not directly exposed in the ventricular wall because the glial layer, in which normal function had broken down, was interposed between the tumor and neuronal nuclei. We, therefore, hypothesized

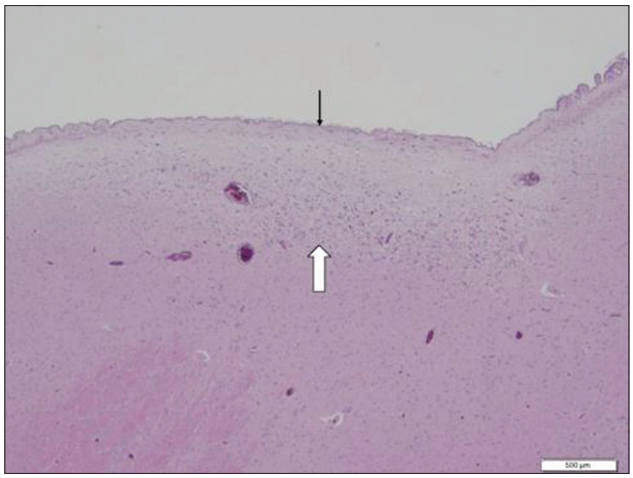

Figure 6: Histopathological findings of a normal hypothalamic specimen taken from an autopsy case in which the cause of death was disease in an organ other than the brain. The top is the third ventricle, lined with an ependymal layer (arrow). Distance from the ependymal layer to the paraventricular nucleus layer (box arrow) is 200–500 μm

that there would be no damage to the hypothalamic neuronal nuclei if dissection proceeded as far as the glial layer, even if perforation of the floor of the third ventricle occurred and petechiae were evident on the lateral surface of the remaining hypothalamus.

Conclusions

The difficulty or otherwise of preserving hypothalamus and pituitary function is determined by the origin of the tumor in the hypothalamus or pituitary stalk, and in how far invasion into this region has progressed. In cases where preservation of pituitary function is determined to be unfeasible during surgery, total resection of the tumor focusing on the histopathology of the tumor dissection surface is the top priority. Resecting the tumor even if this perforates the floor of the third ventricle, and scraping away areas adhering to the lateral wall of the third ventricle together with the glial layer, followed by postoperative hormonal replacement, represents a treatment that offers the best chance of both being curative and leaving the patient with good quality of life.

Even if the pituitary stalk and the floor of the third ventricle are perforated as long as there is continuity of this area, the possibility remains of successfully weaning the patient off hormonal replacement.

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Conflicts of interest

There are no conflicts of interest.

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