The key point of transsphenoidal surgery for infradiaphragmatic craniopharyngioma: Better saddle diaphragm resection

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Research Article

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Abstract

Background Craniopharyngiomas have a high recurrence rate and a poor prognosis, and the key methods for reducing recurrences are unknown. The aim of this study was to explore the key points of microscopic or endoscopic transsphenoidal surgery used to treat infradiaphragmatic craniopharyngiomas.

Methods We reviewed the medical records of patients with infradiaphragmatic craniopharyngiomas who were admitted to Peking Union Medical College Hospital between 2015 and 2018.

Results The main symptoms of patients with infradiaphragmatic craniopharyngiomas included headache, endocrine disorders, decreased vision, or visual field defects. In terms of tumor location, nine patients were completely intrasellar and the remaining 11 patients were intrasuprasellar. Of the 20 patients, 16 patients underwent resection under the microscope and the remaining four patients underwent transsphenoidal endoscopic surgery. Gross total tumor resection was achieved in 12 patients. Six patients underwent saddle diaphragm resection, while the remaining 14 patients were not. Cerebrospinal fluid leaks occurred during surgery in six patients (6/6 saddle diaphragm resection group). Eleven patients with high PRL levels preoperatively all had decreased levels to varying degrees postoperatively and levels returned to normal in eight of these patients. Two patients with diabetes insipidus achieved resolution postoperatively. Visual acuity improved in one patient. After an average follow-up of 26.4 months, eight patients experienced tumor recurrence. Recurrence did not occur in any of the six patients who underwent saddle diaphragm resection (0% vs 57.1%, P=0.0419).

Conclusion The resection of the saddle diaphragm is pivotal in craniopharyngioma removal surgery and is related to tumor recurrence. In comparison to the saddle diaphragm protection group, the resection group is able to achieve a reduced recurrence rate while maintaining acceptable complications.

Background

Craniopharyngioma is a low-grade epithelial tumor with an annual incidence of about 0.5–2.0 patients/million/year[1], and its benign histological characteristic may conceal its biological behavior. The symptoms are closely related to the critical structures it involves[2], in particular the optic chiasm, hypothalamus, pituitary stalk, and vessels in the circle of Willis[3, 4]. Based on its relationship with the saddle diaphragm and the third ventricle, craniopharyngiomas can be divided into different subtypes. Among them, intrasellar craniopharyngioma is unique as its location makes it possible to resect it completely via transsphenoidal surgery and with fewer complications. However, the symptoms of intrasellar craniopharyngioma are more severe than other types because of its close relationship with surrounding structures. It is also not uncommon for clinical surgeons to misdiagnose this type of tumor as a pituitary adenoma. In terms of ideal surgical approaches, endoscopic surgery has unique advantages compared with surgery performed under the microscope. Because of the changeable viewing angle of the endoscope, endoscopic surgery allows better surgical visualization of the suprasellar area and avoids impairing important structures during the procedure[5]. Postoperative complications such as cerebrospinal fluid (CSF) leakage and long-term hyponoalbuminemia occur more frequently in patients with intrasellar craniopharyngioma compared with those with pituitary adenomas. The chance of recurrence often depends on the amount of adhesion between the tumor and surrounding tissues, especially the saddle diaphragm, as well as the proficiency of the surgeon and the surgical approach taken. Unsuccessful resection of the saddle diaphragm is considered to be closely related to recurrence. The broader view of the saddle diaphragm provided by endoscopy may permit better resection of the saddle diaphragm and reduce recurrence rates. We investigated the key points of transsphenoidal surgery used to treat infradiaphragmatic craniopharyngiomas and discovered that resection of the saddle diaphragm is critical in craniopharyngioma removal surgery and is associated with tumor recurrence.

Materials And Methods

The 20 patients in this study were treated at the Department of Neurosurgery in Peking Union Medical College Hospital (PUMCH) between 2015 and 2018. The selection criteria were: 1. Preoperative imaging that indicated the tumor was located in the sellar area, 2. Postoperative histology that confirmed craniopharyngioma, and 3. The first time the patient had undergone pituitary surgery.

After admission, we conducted detailed medical history collection, a physical examination, and enhanced pituitary magnetic resonance image (MRI) for each patient. All patients received neuroendocrinological examinations before and after surgery, including evaluation of the pituitary–thyroid axis, pituitary–gonadal axis, and pituitary–adrenal axis. All patients received one of two types of surgery: endoscopic transsphenoidal surgery or microscopic transsphenoidal surgery. The follow-up interval was 3 months, 6 months, and 12 months after surgery, and then every 6 months thereafter. Follow-up parameters included the patient's quality of life, hormone levels, and presence or absence of recurrence.

Data in this study were collected with Microsoft Excel (2022), and were presented in the form of mean ± standard deviation or as median. Data analyses were performed with SPSS 13.0 statistical software (IBM, Armonk, NY).

Results

Clinical manifestations

We evaluated 20 patients, including 5 men and 15 women. The age of onset ranged from 3 to 65 years old (mean 29.6 years) and the course of the disease ranged from 1 month to 72 months. The main symptoms included headache, endocrine disorders, and decreased vision or visual field defects (Table 2). Fifteen patients had headaches, of which two patients also had vomiting. Among the 15 female patients, 9 had menstrual disorders or amenorrhea, and three had experienced lactation. Nine patients had blurred vision or visual field defects. Diabetes insipidus occurred in four patients. A male patient experienced growth retardation.

Hormone levels preoperative
Prolactin (PRL) levels were elevated preoperatively in 11 patients (male–female ratio 1:10). There were 13 patients with low levels of sex hormones, 7 patients with low levels of thyroid-related hormones, 6 patients with low levels of serum cortisol, and 4 patients with low levels of growth hormone. The range of PRL elevation was 21.77–107.35 ng/ml. Among the 10 women with elevated PRL, 9 had symptoms of amenorrhea or menstrual disorders and 3 had galactorrhea. Preoperative hormone levels are shown in Table 3.

Preoperative imaging
Imaging revealed that the tumor was located completely within the intrasellar region in 9 patients and the intrasuprasellar region in the remaining 11 patients. There were 5 patients with a cystic mass, 2 patients with a solid mass, 12 patients with a mixture of a cystic and solid mass, and 3 patients with calcification. No patients of hydrocephalus occurred preoperatively.

Preoperative diagnosis
The tumors in nine out of the 20 patients were misdiagnosed preoperatively as other diseases including Rathke cleft cysts, pituitary abscesses, and pituitary adenomas.

Intraoperative situation
Of the 20 patients, 6 patients underwent saddle diaphragm resection while the remaining 14 patients did not. Twelve patients received gross total resection (GTR) of the tumor while eight patients received subtotal radical resection (STR). Cerebrospinal fluid leaks occurred during the operation in six patients, all in the saddle diaphragm resection group.

Postoperative recovery
Eleven patients with high PRL levels preoperatively all had decreased levels to varying degrees postoperatively and levels returned to normal in eight of these patients (all female). Estrogen levels increased in seven patients and overall sex hormone levels changed smoothly. Thirteen patients presented with central hypothyroidism postoperatively, newly occurring in six patients. Four patients who developed CSF leakage during endoscopic surgery all recovered without developing intracranial infections. Seven patients developed short-term diabetes insipidus after the procedure, and five of them were new. Two patients of diabetes insipidus resolved postoperatively. Visual acuity improved in one patient (Table 2).

### Table 1

<table>
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<th>Yes (6 patients)</th>
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<td>Intracranial infections</td>
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<td>0</td>
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<td>&gt;0.9999</td>
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<tr>
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<td>6</td>
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<tr>
<td>Recurrence*</td>
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<td>0.0419</td>
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<tr>
<td>Hormone replace therapy</td>
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<td>4</td>
<td>&gt;0.9999</td>
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</table>

*Incomplete surgical resection of the tumor was also classified as recurrent patient.

P < 0.05 was considered statistically significant.

Pathology
The histopathological analysis of the tumors in all 20 patients confirmed craniopharyngiomas, of which two patients were classified as squamous epidermal type, one patient was ameloblastic type, and the rest were not classified.

Follow up
Seventeen patients are still being monitored while the remaining three were lost to follow-up. The follow-up period ranged from 3 months to 60 months (average 27.31 months). Four patients with hormonal disorders had hormone levels return to normal postoperatively, while five patients required hormone replacement therapy (HRT) after surgery. Recurrence did not occur in any of the patients who received GTR, regardless of the surgical method (Table 2). The following Fig. 1 shows MR images from patient 2, who underwent transsphenoidal endoscopic surgery and saddle diaphragm resection. During the follow-up period of 51 months, there was no evidence suggesting recurrence.
<table>
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<th>Patients</th>
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<th>Surgery</th>
<th>Resection of saddle diaphragm</th>
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<td>60</td>
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<td>Yes</td>
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<td>No</td>
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</table>

CP craniopharyngioma; PA Pituitary adenomas; PC Pituitary cyst; RC Rathke cyst; PA Pituitary abscess; PT Pituitary tumor; HRT hormone replace therapy; M male; F female; GTR gross total removal; STR Subtotal resection; ND not determined.
Cranioopharyngioma is a rare embryonic malformation arising from the squamous epithelial remnants of Rathke's pouch. A bimodal distribution by age has been found, with peak incidence rates in children from 5–14 years of age and in older adults from 50–74 years of age[2].

There are many ways to classify craniopharyngiomas. In terms of location, they can be divided into three types based on their relationship to the sellar region: 1) suprasellar craniopharyngiomas, 2) intra- and suprasellar craniopharyngiomas, and 3) purely intrasellar craniopharyngiomas[6]. Infra diaphragmatic craniopharyngiomas are relatively rare compared with the supradiaphragmatic type and account for approximately 5% of patients[7]. In this study, nine patients were purely intrasellar craniopharyngiomas, and the rest were intrasuprasellar craniopharyngiomas. When the tumor invades and gradually impinges on the sellar region, patients develop visual disorders. Infra diaphragmatic craniopharyngiomas can induce more severe symptoms compared with supradiaphragmatic craniopharyngiomas, including signs of endocrine dysfunction and visual disturbances, because of the compression of the pituitary gland and surrounding structures. Pathologically, there are two main types of craniopharyngiomas: adamantinomatous and papillary. The former usually occurs in children and are accompanied by calcifications. The latter are more likely to appear in adults[2, 6]. In childhood and adolescents, adamantinomatous craniopharyngiomas with cyst formation are more common.

Obtaining a definitive diagnosis for cystic lesions in the sellar region is difficult and the diagnosis can only be confirmed by pathological exam during and after the procedure. However, craniopharyngiomas cannot be ruled out as the potential cause of hyperintensity in a T1-weighted (T1WI) MRI. A craniopharyngioma typically appears as a solid-cystic lobulated lesion with reticular enhancement of the solid portion on an MRI[8]. Cystic infradiaphragmatic craniopharyngiomas, which are relatively rare, often manifest as homogeneous, high signal intensity lesions on T1WI without enhancement, and the signal intensity is similar with T1WI contrast enhancement scans[7]. Cystic infradiaphragmatic craniopharyngiomas are often confused with Rathke cleft cysts, pituitary apoplexy, and arachnoid cysts[9].

Transsphenoidal surgery can provide a clearer and wider vision of the surgical field with fewer complications compared with transcranial surgery[10, 11]. Wang et al. suggest that, though transsphenoidal surgery can impair the pituitary gland, it has great advantages in improving hyperprolactinemia and alleviating visual impairment and defects. At the same time, it is associated with a low recurrence rate[7]. The most popular approaches to transsphenoidal surgery are microscopic and endoscopic surgery.
Endoscopic transsphenoidal surgery has become a reliable treatment method for primary and recurrent craniopharyngiomas in the last decade[12]. For infradiaphragmatic craniopharyngiomas that originate from the pituitary stalk, endoscopic surgery is an efficient way to dissect the adhering and surrounding vital structures. According to a retrospective study of 226 patients[13], intrasellar craniopharyngiomas carry the lowest probability of hypothalamic dysfunction after radical resection compared with the other types of craniopharyngiomas. Over the last decade, neurosurgeon preference for endoscopy has increased significantly[14]. The most obvious advantage of endoscopic surgery is providing a panoramic view of the operating field with changeable angles, especially in the suprasellar area, which allows surgeons to obtain a precise view of the surrounding critical structures[5, 15, 16]. With the help of angled lens endoscopes, surgeons can even obtain direct visualization of the suprasellar region[17]. This better visualization allows the normal pituitary tissue to be more easily distinguished from the cystic walls of the tumor and better saddle diaphragm resection can be achieved without the need to blindly rely on surgeon experience. In our study, six patients underwent saddle diaphragm resection, while the remaining 14 patients were not. In terms of average GTR rate, the resection group was 100%, while the other group was 42.9% (P = 0.0419). And there was significant difference in the recurrence rate between the two groups (0% vs 57.1%, P = 0.0419). In comparison to supradiaphragmatic craniopharyngioma, infradiaphragmatic craniopharyngiomas are very uncommon, accounting for around 5% of cases[7]. Future advancement of this study requires the evaluation of more patients.

Ogawa et al. demonstrated that pituitary function can partially recover even after pituitary stalk removal[18] and aggressive tumor removal can prevent tumor regrowth. In this study, we found the postoperative complications of the two surgical methods did not differ significantly (Table 1). Thus, as the goal is to remove as much of the tumor as possible to reduce the recurrence rate, better saddle diaphragm resection is recommended. Intraoperative CSF leakage occurred in 100% of patients in the saddle diaphragm resection group, while the rate within the saddle diaphragm preservation group was 0% (P < 0.0001). However, even if the probability of cerebrospinal fluid leakage increases, this is likely an acceptable cost given the decreased risk of tumor recurrence and that the leakage can be addressed with fascia lata, muscle, or fat implantation [19]. In addition, not all patients with cerebrospinal fluid leakage develop intracranial infections. Of the 6 patients in the saddle diaphragm resection group with cerebrospinal fluid leakage, none have progressed. According to a prospective, multicenter, controlled research study of nonfunctioning pituitary adenomas, less experienced endoscopic surgeons can surprisingly achieve similar GTR rates compared with experienced microscopic surgeons [20]. Endoscopic surgery has less of a learning curve and it is easier for less experienced surgeons to achieve good results in a shorter time. This study also found that in experienced hands, endoscopic surgery carries a low complication rate, which was consistent with our results.

If it is impossible to completely remove tumors or if gross resection may result in severe side effects, then postoperative radiation can be considered to improve the prognosis[21–24]. Recent research has proven that limited surgery and photon-based conformal radiation therapy achieve excellent tumor control[25]. For cystic craniopharyngiomas, [32P] intracavitary irradiation is recommended[26].

Conclusions

The key to successful microscopic or endoscopic transsphenoidal surgery for infradiaphragmatic craniopharyngiomas lies in saddle diaphragm resection. Due to the recurrence risk associated with craniopharyngiomas, a gross complete resection is crucial for both patients and surgeons. In this research, the saddle diaphragm resection group had lower recurrence rates than the protect group, and the complications were not excessive. With the advancement of repair technology, cerebrospinal fluid leakage induced by total resection of the saddle diaphragm will be better healed. Endoscopies can provide a panoramic view of the operative field and have a shorter learning curve than microscopes. In light of this, they may eventually play a pivotal role in the surgical treatment of infradiaphragmatic craniopharyngiomas.

Declarations

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Conflicts of interest The authors have no conflicts of interest to declare.

Authors’ contributions Qi Liu Writing—original draft. Xiaokun Chen Writing—original draft. Xinjie Bao Conceptualization, Writing—review & editing. Yong Yao Resources, Writing—review & editing. Kan Deng Resources. Ming Feng Resources. Wei Lian Resources. Bing Xing Conceptualization. Renzhi Wang Conceptualization.

Ethics approval and consent to participate Informed consent was obtained from all individual participants or their parents and/or legal guardians included in the study. This retrospective study was approved by the Ethics Research Board of Peking Union Medical College Hospital (PUMCH). All experiments and methods were performed in accordance with relevant guidelines and regulations.

Consent to publish Patients signed informed consent regarding publishing their data.

Availability of data and materials The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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References


Figures
Figure 1

Magnetic resonance (MR) images obtained from Patient 2, who received transsphenoidal endoscopic surgery and saddle diaphragm resection. (AB) Preoperative coronal and sagittal T1-weighted with contrast MR images showed high signal intensity and a snowman-like appearance in the intrasuprasellar region. Coronal and sagittal T1-weighted with contrast MR images 5 days (CD), 6 months (EF), 36 months (GH), and 51 months (IJ) after surgery showed no recurrence.