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# Extended endoscopic endonasal approach for pituitary adenoma: a single-center experience of 171 patients

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## Abstract

**Background:** Pituitary adenoma (PA) is a common intracranial tumor and surgical treatment is considered to be the best treatment for most patients. The extended endoscopic endonasal approach (EEEA) has been used to treat increasing numbers of patients with PA in recent years. We conducted this study to evaluate the safety and efficacy of this approach for PA resection.

**Methods:** We performed a retrospective analysis of all patients who underwent an EEEA to remove PA by a binostril, four-handed technique between October 2013 and April 2016 in our department. The medical information of the patients including gender, age, tumor size, hormone level, clinical outcome, and complications were collected and analyzed.

**Results:** From a total of 593 pituitary adenoma surgeries, 171 patients (101 male and 70 female, mean age  $47.4 \pm 12.8$  years) underwent EEEA, including 96 with functional adenomas (56.14%) and 75 with nonfunctional adenomas (43.86%). The most common symptoms were headache and vision change. Gross total resection was achieved in 126 patients (73.68%). Common complications were hyposmia or anosmia, diabetes insipidus, hypopituitarism, postoperative cerebrospinal fluid leak, cerebral hemorrhage, and epistaxis. The mean duration of follow-up was 14.6 months (range: 6–31 months).

**Conclusions:** The application of EEEA for PA resection by a binostril, four-handed technique provided great surgical freedom with minimal invasion, and resulted in few complications. EEEA is a secure and effective surgical method that could be used for the majority of PAs.

**Keywords:** Pituitary adenoma, Endoscope, Extend endoscopic endonasal approach

## Background

Pituitary adenoma (PA) is common in the general population. According to a previous epidemiology study, about 16.7% of the general population show changes in the pituitary gland [1]. PA can be classified by diameter and divided into microadenomas (<1 cm), macroadenomas (1–4 cm), or giant adenomas (>4 cm) [1, 2]. Depending on endocrinological status, PA can be classified as nonfunctioning or functioning. Functioning PA may be further divided into prolactin-secreting (PRL), growth hormone-secreting (GH),

gonadotropin-secreting, adrenocorticotrophic hormone-secreting (ACTH), thyroid-stimulating hormone-secreting (TSH), and multiple hormone-secreting forms.

Surgical treatment is considered the primary therapy in nonfunctioning PA, GH-secreting, ACTH-secreting, gonadotropin-secreting, and TSH-secreting PAs [3]. For PRL-secreting PA, while medical therapy constitutes the primary treatment, surgery is an option for patients who are intolerant or resistant to drugs, have pituitary apoplexy, or tumor progression under medical therapy [3–5]. Surgery of PA has improved over the last 100 years to reduce trauma and complications, and improve the postoperative outcome. Horsley reported the first resection of a pituitary tumor by open craniotomy in 1887 [6]. Schloffer et al. first described the transsphenoidal

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approach in a sellar tumor in 1907 [7]. In the 1960s, the operation microscope was introduced during transsphenoidal procedures by Hardy and was quickly adopted for clinical neurosurgical practice [8]. Since then, the use of a transsphenoidal microscope for pituitary surgery is considered the gold standard [9]. In 1963, Gerard Guito introduced the use of an endoscope during transsphenoidal procedures to provide an overview of the contents of the sellar turcica [10]. In 1992, Jankowski et al. first used endoscopy for the resection of PA, and pure transsphenoidal endoscopic PA surgery was described later by Jho and Carrau [11, 12]. Over the last two decades, following the development of optical techniques, endoscopic endonasal surgery for PAs has been progressively accepted by many neurosurgeons and has become popular in many clinical centers. Increasing numbers of neurosurgeons now choose the endoscopic endonasal approach as the first option to resect PA, due to the wider visualization and reduced trauma [13–16]. However, the standard transsphenoidal approach fails to expose PAs invading the anterior cranial base, cavernous sinus, and clivus [17]. Therefore, continuous efforts have been made to improve surgical techniques. Several of these attempts have reported the application of extended endoscopic endonasal approach (EEEA), which removes the PA, with minimal invasiveness and low numbers of complications [17, 18].

## Methods

### Study Design

From October 2013 to April 2016, those patients who underwent an EEEA for a PA surgery in the Neurosurgery Department of Wuhan Union Hospital met our inclusion criteria. All the patients underwent an assessment of preoperative endocrinologic and neuroimaging (including magnetic resonance imaging [MRI] with contrast of pituitary and computed tomography [CT] of nasopharynx). An endocrinologic test, performed before and after the operation, consisted of sexual hormones, cortisol at 8 AM and 4 PM, free triiodothyronine, free thyroxine, TSH, and GH. The patients were followed-up from 6 to 31 months, (mean, 14.6 months). The medical information of the patients were reviewed to collected demographic data, including gender, age, clinical symptoms, hormonal level, tumor size, clinical outcome, and complications.

### Surgical technique

Under general anesthesia, the patient was placed in the supine position without routine rigid fixation of the head. The surgeon and the assistant were both positioned on the right side of the patient. After strict sterilization of the nasal cavity and oral cavity, cotton pieces soaked with adrenalin were used to contract

blood vessels and enlarge the nasal cavity. The operation is usually performed using a binostril route with a 0° rigid endoscope. Once the endoscope is inserted into the nostril, the inferior turbinate and nasal septum is visible. Then the middle turbinate was lateralized to increase the surgical corridor, and the sphenoid sinus ostium, a key anatomic landmark, could be seen 1.0–1.5 cm above the sphenoethmoid recess. The posterior nasal septum was removed to link the bilateral nasal cavities and increase the working space, and the anterior wall and partial septum of sphenoid sinus were removed together (Fig. 1).

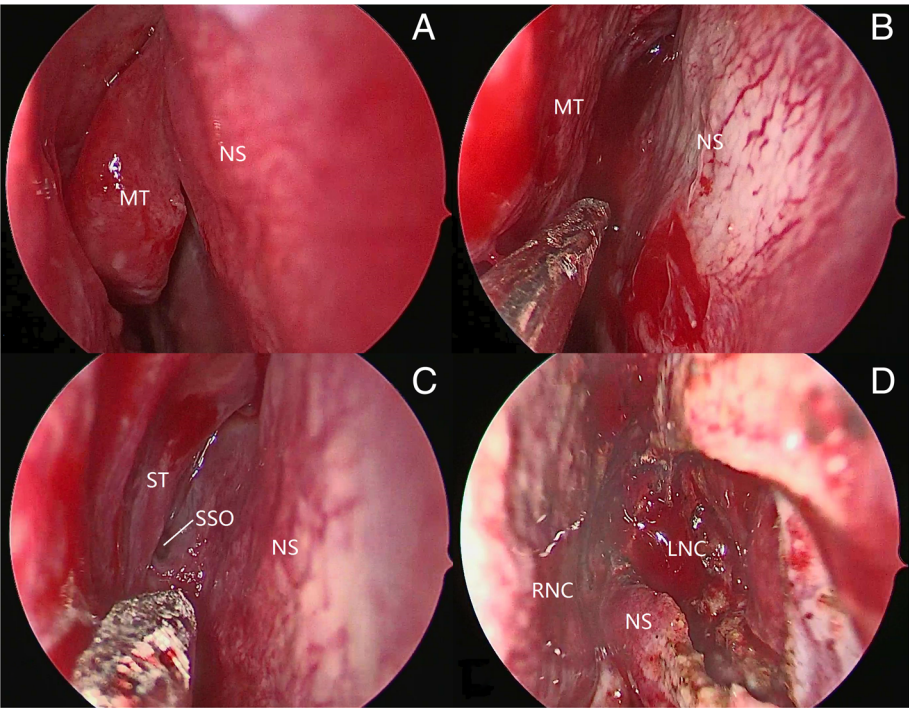
After removal of the residual septum of the sphenoid sinus, the dura was opened with a cruciate incision, and the tumor was resected piece-by-piece with a curette, tweezers, and aspirator. After removal of the tumor, we used gelfoam to block the surgical cavity, and a neuro-patch was placed within the dural defect. If a postoperative cerebrospinal fluid (CSF) leak was foreseeable, more material is used to reconstruct the skull base, including autologous fascia and fat of the muscoli quadriceps femoris, vascularized pedicled nasoseptal flap, and fibrin glue. Finally, a meche and a catheter with an aqueous capsule were used to support the skull base, and were removed several days later (Fig. 2).

## Results

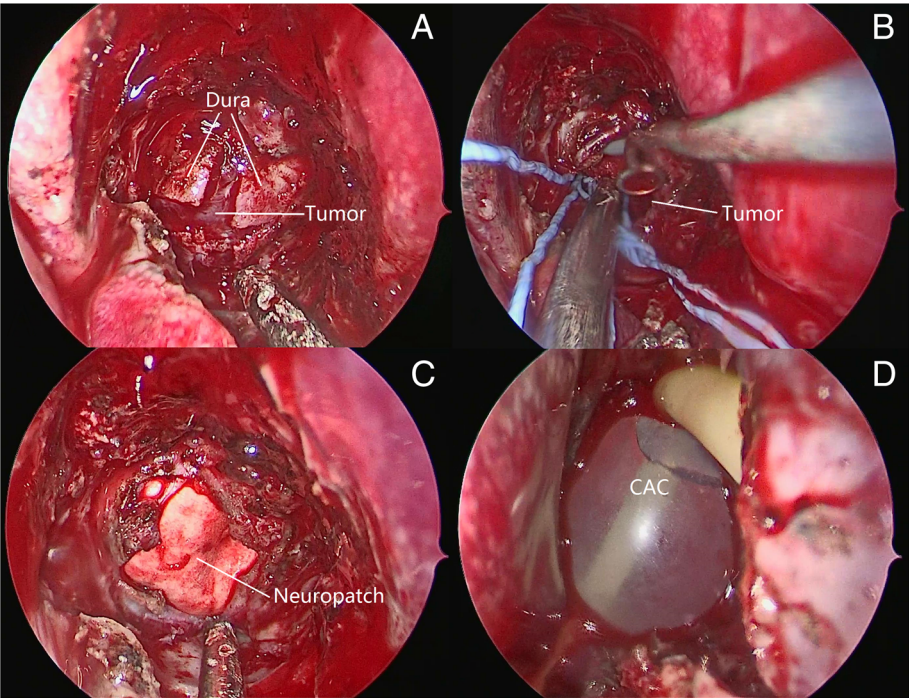
The study sample comprised 101 men and 70 women, with a mean age of  $47.4 \pm 12.8$  years with a range of 15–71 years. All the patients with PRL-secreting PA had failed medical therapy before surgery or had a pituitary apoplexy. The mean tumor volume in our study was  $8.752 \pm 12.53$  cm<sup>3</sup>, with 20 microadenomas (11.70%), 133 macroadenomas (77.78%) and 18 giant adenomas (10.52%).

The main symptoms at diagnosis were headache (65 patients, 38.01%), visual impairment (visual loss, diplopia, and visual field defect in 64 patients, 37.43%), menstrual disorder or lactation (27 patients, 15.79%) and acromegaly (9 patients, 5.26%). In addition, 18 patients (10.53%) were diagnosed incidentally without any obvious symptoms (Table 1).

Gross total resection (GTR) was achieved in 126 patients (73.68%), including 20 microadenomas, 102 macroadenomas, and 4 giant adenomas. Based on the functional classification, GTR was achieved in 68 functional adenomas (28 in PRL-secreting, 7 in GH-secreting, 5 in gonadotropin-secreting, 2 in ACTH-secreting, 2 in TSH-secreting and 24 in multiple hormone-secreting) and 58 nonfunctional adenomas (Table 2). There were 4 patients who underwent a second microscope or endoscopic surgery and 11 patients received postoperative gamma knife treatment.



**Fig. 1** The route of the EEEA at the nasal rhinal stage. **a:** The middle turbinate (MT) and nasal septum (NS). **b:** The middle turbinate has been lateralized. **c:** The sphenoid sinus ostium (SSO) is present between the superior turbinate (ST) and nasal septum. **d:** After resection of the partial nasal septum, the right nasal cavity (RNC) and left nasal cavity (LNC) were linked together



**Fig. 2** Removal of the tumor and reconstruction of the skull base. **a:** The dura was opened with a cruciate incision. **b:** The tumor was resected with a curette. **c:** The application of a neuropatch to repair the dura defect. **d:** A catheter with aqueous capsule (CAC) was used to support the skull base



**Table 1** Symptoms of the patients

Symptoms	Number	Percent
Headache	65	38.01
Visual impairment	64	37.43
Menstrual disorder or lactation	27	15.79
Silent	18	10.53
Acromegaly	9	5.26

The symptoms of 144 patients (95.36%) were significantly improved or had disappeared in 151 patients (20 patients did not have any obvious symptoms). Surgery-related complications were reported in 55 cases (32.16%), including hypopituitarism (6 patients, 3.51%), postoperative CSF leak (3 patients, 1.75%), diabetes insipidus temporary (14 patients, 8.19%), hyposmia or anosmia (24 patients, 14.04%), cerebral hemorrhage (4 patients, 2.34%), and epistaxis (4 patients, 2.34%, Table 3). The most common postoperative complication was hyposmia or anosmia. All the patients underwent an examination of pituitary relative hormone within 1 week after operation. Relative hormone levels were reduced in 40 patients (23.39%), but of these, only 6 required long-term hormone replacement therapy, because the other patients recovered normal hormone levels quickly. Hyposmia and anosmia also slowly recovered in most patients. Obvious postoperative CSF leak occurred in 3 patients, one of which underwent a successful repair surgery, and two others who recovered with expected treatment, and all of them recovered with no intracranial infection. The autologous fascia was used in 20 patients to avoid CSF leak. We also observed one death in our study.

**Table 2** Rate of tumor gross total resection

Types	Number	Number of GTR	Percent
Nonfunctioning adenomas	75	58	77.33
PRL-secreting adenomas	37	28	75.68
GH-secreting adenomas	14	7	50.00
Gonadotropic hormone-secreting adenomas	9	5	55.56
ACTH-secreting adenomas	3	2	66.67
TSH-secreting adenomas	2	2	100
Multiple hormone-secreting adenomas	31	24	77.42
Microadenomas	20	20	100
Macroadenomas	133	102	76.69
Giant adenomas	18	4	22.22
Total	171	126	73.68

PRL prolactin, GH growth hormone, ACTH adrenocorticotrophic hormone, TSH thyroid-stimulating hormone

**Table 3** Postoperative complications

Complications	Number	Percent
Hypopituitarism	6	3.51
CSF Leak	3	1.75
Diabetes insipidus temporary	14	8.19
Diabetes insipidus permanent	0	0.00
Hyposmia or anosmia	24	14.04
Cerebral hemorrhage	4	2.34
Epistaxis	4	2.34

CSF Cerebrospinal fluid

## Discussion

### Surgical technique

Over the last two decades, surgery with an endoscopic approach for PA has come into prominence and slowly reached favor globally. Compared with the traditional microscope-based approach, the endoscopic approach provides better visualization, decreased invasiveness, and fewer complications, particularly for the removal of extrasellar and parasellar tumor extension [9, 14]. The EEEA provides the possibility to resect the tumor with suprasellar extension, but at the same time, causes additional bone resection and more trauma than the standard surgery. Youssef et al reported that EEEA was not applicable for the safe removal of PAs invading the cavernous sinus [19]. However, other studies using EEEA have reported a wider visualization and working space, enabling the resection of PAs located in the suprasellar regions, cavernous sinus, and clivus safely and effectively [18, 20, 21]. The EEEA always uses the binostril route, which requires at least two surgeons. Sheng Han et al argued that a mononostril technique was adequate for the endoscopic resection of most PAs with moderate extension [22]. However, Elhadi et al reported that the binostril approach provided better surgical freedom than the mononostril approach from a study of 8 silicon-injected cadaveric heads [23]. Guodao et al performed a systemic review and meta-analysis and found the binostril approach caused less pituitary disturbance and fewer hospitalization days, whereas the mononostril approach showed less trauma of the nasal cavity [24].

Our department started the transition from microscopic to endoscopic transsphenoidal surgery for PA from October 2013. In our experience, the application of EEEA to resect PA by a binostril, four-handed method is safe and effective. Although the standard transsphenoidal approach is adequate for the majority of PAs, the binostril approach has more extensive indications and benefits the management of bleeding complications during the procedure with more working space. This may be more important to giant adenoma and invasive adenoma. Generally, the standard transsphenoidal approach can resect microadenoma well. But for the tumor located



within pituitary, the EEEA can offer better visualization to find and resect the tumor.

It is critical to understand there is a steep learning curve for EEEA. The surgeon must be skilled in the equipment used in this approach and become accustomed to the image distortion and the loss of stereoscopic vision. Recently, many clinical centers have used a three-dimensional (3D) endoscope view to improve the visualization of anatomical structures and their relationships. This 3D endoscope may reduce the learning curve of the surgeon, and provide stereoscopic vision and depth perception [25, 26].

### GTR

The GTR rate of endoscopic surgery for PA varies widely from 62% to 94%, with most reports around 70% [14, 15, 27–32]. In our study, the assessment of resection was determined by the postoperative MR images, and GTR was achieved in 126 patients (73.68%), similar to that reported by other studies. About 25% patients had a subtotal or partial resection for the following reasons: huge size or tough texture of the tumor; rich blood supply; tumor was partitioned by septa; and parasellar and suprasellar extension. Jain et al reported that tumor size and volume, as well as parasellar and suprasellar extensions were associated with surgical outcome. They found that the favorable factors for total removal were a tumor volume less than 5 cm<sup>3</sup> with no parasellar and suprasellar extension [33]. Qiuhan et al argued that soft lesions were better suited to an endoscopic approach than hard, solid tumors [34].

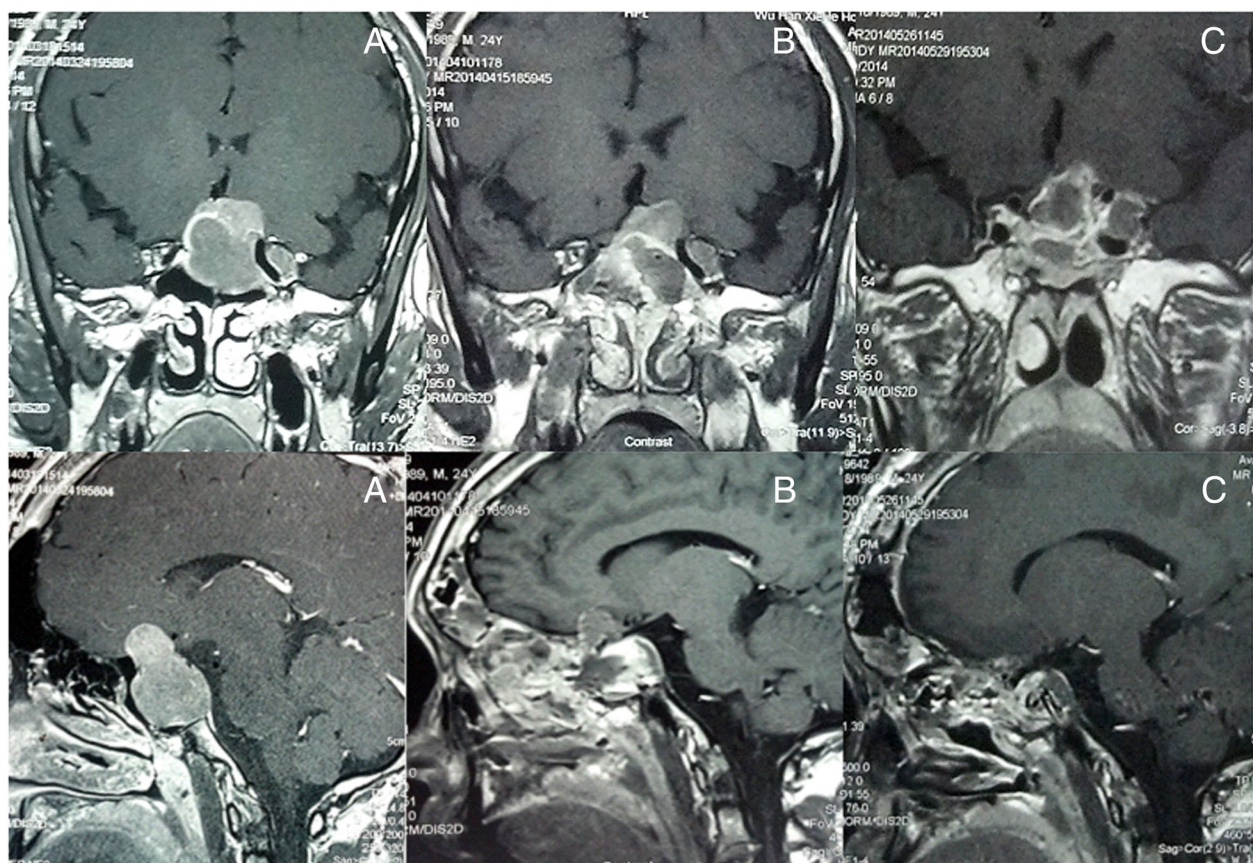
Total removal of all the PA is discouraged because it may increase the incidence of serious complications,

especially for some tumors that have invaded the cavernous sinus or encased the internal carotid arteries (as shown in Fig. 3). Gondim et al reported a patient with a macroadenoma and right side hemiparesis presented in the first postoperative day, with a hematoma in the left side of the pons found by MRI. The patient recovered partially at 6 months after surgery, but still presenting with a mild weakness on the right side. The author believed this event might have been associated with the attempt to achieve a GTR of the retrosellar at the position of the lesion [29].

At the beginning of our learning curve, 2 patients had a second microscopic surgery to resect the residual tumor. The first was a 23-year-old man with a GH-secreting macroadenoma (length × width × height: 3.1 × 3.8 × 3.8 cm, volume: 22.3 cm<sup>3</sup>). The tumor had grown upwards and invaded the suprasellar region. We performed an endoscopic surgery to resect the lower section of the tumor and the residual section was resected by microscopic surgery 7 weeks later. This patient also underwent a gamma knife treatment 10 months after the first surgery and had an ideal outcome (Fig. 4). The other patient was a 46-year-old woman who had a non-functional giant adenoma (length × width × height: 2.7 × 5.8 × 5.3 cm, volume: 41.5 cm<sup>3</sup>). She underwent a similar treatment and recovered well. There were 2 patients who had a second endoscopic surgery, both of which had a tumor too big to resect totally from one surgery. The second surgeries were similar to the first, and they both recovered without problems. 11 patients in our series underwent a postoperative gamma knife treatment, which is a safe and effective treatment for PA [35, 36]. In our opinion, EEEA surgery and



**Fig. 3** MRI with contrast image of a female patient with a giant adenoma. A nonfunctional adenoma with giant volume, invaded the cavernous sinus and the third ventricle, and encased the internal carotid artery



**Fig. 4** Coronal and sagittal MRI images of a patient who underwent a second surgery. **a:** MRI image before surgery, showing the anterior cranial base was invaded by the macroadenoma; **b:** MRI image after the first surgery when the tumor has been partly resected; **c:** MRI image after the second surgery, showing the tumor was subtotal removed

subsequent gamma knife treatment is a good way to treat tumors that are difficult to resect totally.

### Complications

Postoperative CSF leak has always been an intractable problem of transsphenoidal surgery. In our study, postoperative CSF leak was observed in 3 patients (1.75%). Ciric et al reported that 3172 neurosurgeons were asked about the complications of transsphenoidal surgery by questionnaire and 985 reported they had performed transsphenoidal surgery. The neurosurgeons were divided based on the number of surgeries performed, <200, 200–500, and >500. The postoperative CSF leak index for these groups was 4.2%, 2.8%, and 1.5%, respectively [37]. Abtin tabaee et al conducted a meta-analysis of 821 patients who underwent an endoscopic approach, and showed the rate of CSF leak varied from 0%–27% [14]. Other published studies reported rates of CSF leak of 0.83%–10.3%, which are comparable with our study [29, 32, 38–40]. We believe the most important measure to avoid this complication is the adequate repair of the sella floor.

Diabetes insipidus is a common complication after PA surgery. In previous studies, the rate of temporary and permanent diabetes insipidus was 0–22% and 0–5%, respectively [14, 29, 32, 38–40]. There were 14 patients (8.19%) with temporary diabetes insipidus in our study, and no permanent diabetes insipidus cases were observed. Temporary diabetes insipidus may be a result of the temporary dysfunction of vasopressin-producing neurons caused by surgical trauma. This can be precluded by avoiding manipulation of the pituitary stalk [37].

The rate of other complications reported in our study including hypopituitarism, hyposmia or anosmia, cerebral hemorrhage and epistaxis, may decrease with an increase in surgeon experience of the transsphenoidal procedures; a gentle technique and careful dissection may be key to reducing such complications.

### Death

There was one death in our series, a 50-year-old woman suffered from bilateral vision loss for 1 year. She had a nonfunctional macroadenoma and underwent an EEEA surgery. She became delirious 10 h after the surgery. A



cranial CT was performed immediately and showed a giant hematoma in the sellar and suprasellar regions. Then the patient underwent an emergency bilateral ventricular drainage but it was not effective. Without any sign of improvement, her family gave approval to stop treatment 4 days later. The cause of the hematoma might have been deficient hemostasis during the operation. This was a painful lesson for us and promoted us to try our best to avoid any complications.

## Conclusion

The application of EEEA for PA resection by a binostril, four-handed technique can provide wider visualization and working space, and reduce trauma and complications. It is a secure and effective surgical method that can be used for the majority of PAs.

## Abbreviations

3D: Three-dimensional; ACTH: Adrenocorticotrophic hormone; CAC: Catheter with aqueous capsule; CSF: Cerebrospinal fluid; CT: Computed tomography; EEEA: Extended endoscopic endonasal approach; GH: Growth hormone; GTR: Gross total resection; LNC: Left nasal cavity; MRI: Magnetic resonance imaging; MT: Middle turbinate; NS: Nasal septum; PA: Pituitary adenoma; PRL: Prolactin; RNC: Right nasal cavity; SSO: Sphenoid sinus ostium; ST: Superior turbinate; TSH: Thyroid-stimulating hormone

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## Availability of data and materials

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

## Authors' contributions

HZ conceived of the study, and participated in its design; XJ participated in the design of the study and performed the operations and helped to draft the manuscript; ZL drafted the manuscript and participated in the perform of statistical collection and analysis; XH participated in the perform of statistical collection and analysis; HW participated in the perform of the operations and helped to collect the data, all authors read and approved the final manuscript.

## Competing interests

The authors declare that they have no competing interests.

## Consent for publication

All patients in our study consented to publish those data, and we can offer the copy of the form.

## Ethics approval and consent to participate

We have submitted our study plan to Medical Ethics Committee of Tongji Medical College of Huazhong University of Science and Technology, they confirmed that the ethics approval was not necessary for a retrospective study which just used to medical research.

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