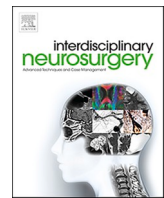




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Research Article

## Endoscopic endonasal approach for pituitary adenomas: Results from a multidisciplinary management

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### ABSTRACT

**Background:** Endoscopic endonasal approach (EEA) has gained increasing acceptance in the world; however, pituitary adenomas require multidisciplinary management for good outcomes. The aim of this study is to report the results of this management of a consecutive series of patients who underwent a purely endoscopic endonasal approach for pituitary adenomas resection in our hospital and compare them to other series.

**Methods:** A retrospective review of clinical and radiographic records of 80 consecutive patients with pituitary adenomas who were operated on using an EEA between 2011 and 2019 was performed. The patients' clinical, ophthalmologic, endocrinologic and radiographic outcomes were evaluated.

**Results:** 57% were women and 43% men. The age ranged from 10 to 79 years. 72 tumours (90%) were macroadenomas; in 19 patients (23.75%) the cavernous sinus was invaded. There were 58 non-functioning adenomas and 17 growth hormone secreting, 4 prolactin-secreting, and 1 thyroid-stimulating hormone-secreting adenomas. Gross total resection was achieved in 76.2% of tumours without cavernous sinus invasion. Of the 53 patients presenting with visual loss, 47 (88.6%) improved or normalized. The remission rates with EEA alone were 58% in the GH-secreting adenomas and 75% in the prolactinomas group. Complications included CSF leak in 12.5%, new hormonal deficit in 18.75%, epistaxis in 6.25%, sella hematoma in 3.75% and neuroinfection in 1 patient (1.25%). We did not have mortality. The follow-up was from 6 to 87 months.

**Conclusions:** A multidisciplinary management is required for the adequate treatment of pituitary adenomas. With good surgical training, the EEA is safe and effective around the world. Our results are similar compared with those reported in previous series of microscopic or endoscopic approaches.

### 1. Introduction

Gerard Guiot introduced the endoscope to transsphenoidal surgery in the early 1960s [14]; however, Jho and Carrau reported the first clinical series of purely endoscopic pituitary surgery in 1997 [19]. The subsequent reports contributed to the refinement of the technique and detailed anatomical knowledge from the endonasal perspective [4,20–22,31].

In recent years, the endoscopic endonasal approach (EEA) has gained increasing acceptance due to the comparable results with the traditional transsphenoidal microscopic surgery [1,6–7,9,13,16,29,30].

The advantages of using the endoscope, such as a close-up view of the anatomy, wider surgical visualization, variable working angle and lighting of the surgical field, made many surgeons gradually shift towards an endoscopic approach for pituitary adenomas and other parasellar or suprasellar tumours.

The aim of this study is to report the results of a multidisciplinary management of pituitary adenomas undergoing to a pure EEA in a single center and to assess safety and efficacy when compared with previous reports.

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## 2. Materials and Methods

We performed a retrospective review of 80 consecutive patients with pituitary adenoma, who underwent purely EEA between January 2011 and June 2019 in our institution.

Patients' demographics, clinical and radiographic characteristics and postoperative course were obtained from the medical records.

Endocrinology assessment was performed before and after surgery including a complete pituitary function panel reviewed by two endocrinologists from our center. In acromegaly cases, remission was defined in accordance with the latest guidelines [11].

Ophthalmologic examination was also routinely performed before surgery and every 6 months after the procedure by different ophthalmologic centres in the city. The exam included a fundoscopy, visual acuity, colour acuity, visual fields and pupillary reflex. The visual outcome after surgery was expressed as improved, unchanged or worse when compared to the pre-operative level.

Radiographic evaluation consisted of CT scan of the paranasal sinus for a detailed study of the bony anatomy. Magnetic resonance imaging (MRI) with gadolinium of the sella was made in all the patients preoperatively and postoperatively. The Hardy-Vezina [17] and Knosp [23] scales were used to determine the suprasellar extension and prediction of cavernous sinus invasion (CSI), because "true CSI" was not established intra-operatively.

The extent of resection was defined by a radiologist of our hospital as gross total resection (GTR); near total resection (NTR > 95%); subtotal resection (STR 75–95%); and partial resection (<75%) according to the MRI 3 months after surgery.

Statistical analysis was performed using SPSS (version 22.0).

### 2.1. Surgical Technique:

The procedure performed by a surgical team composed of an ENT surgeon (MJ) and a neurosurgeon (SL). A detailed description of the technique is beyond the scope of this article, but the systematized steps of the procedure are summarized:

- Use of 0 and 30-degree endoscopes.
- Resection of the right middle turbinate.
- Creation of the vascularized pedicle nasoseptal flap (since 2013).
- Removal of the posterior septum.
- A two-nostril three/four-hand technique is employed.
- A wide bilateral sphenoidotomy is performed.
- Drilling of the inter-osseous septa and the sella floor.
- Dura opening in a rectangular or cross fashion.
- Tumour resection using a combination of curettes and suction.
- Haemostasis control and reconstruction.
- Intraoperative image guidance has been used since 2016.

### 2.2. Immediate post-operative care:

The patient is taken to the regular hospital room; intensive care unit is usually not necessary. On the day after the operation the patient undergoes to CT scan of the sella and pituitary hormone panel. The patients are discharged one or two days after the procedure, if CSF leak is ruled out.

## 3. Results

Of the 80 patients, 46 (57%) were female and 34 (43%) were male. The age ranged from 10 to 79 years of age, with a mean of 48 years. Seventy-two patients had a macroadenoma (90%) and 8 patients had a microadenoma (10%). The suprasellar extension and the cavernous sinus invasion based on magnetic resonance imaging are summarized in the Tables 1 and 2.

**Table 1**  
Distribution of patients according Hardy-Vezina scale

	0	A	B	C	D	E
I	7					1
II	4	7				6
III	1	2	1			1
IV		5	17	15	3	11
V						

**Table 2**  
Distribution of patients according Knosp grade

Knosp Grade	Number
0	43
1	18
2	8
3	6
4	5

### 3.1. Clinical Presentation:

The most common symptom was due to mass effect, which produced a gradual visual deficit in 44 patients (55%), clinical evidence of hormonal disturbances in 16 patients (20%), pituitary apoplexy in 8 patients (10%), headache in 7 patients (8.75%), III CN palsy in one patient. In 4 patients the diagnosis was incidental.

### 3.2. Previous Treatment:

Five patients presented with residual tumours that had been previously operated on in another institution. Before surgery, 9 patients with non-functional tumours received treatment with cabergoline and one patient with acromegaly received octreotide; endocrinologists outside our hospital had treated all of them.

### 3.3. Surgical results (Tables 3 and 4)

Gross Total Resection was achieved in 76.2% of adenomas without cavernous sinus invasion. Cavernous sinus compromise according radiographic evaluation ( $p = < 0.001$ ) and medical treatment before surgery with cabergoline ( $p = 0.007$ ) negatively affected the extension of resection. Suprasellar extension (Hardy-Vezina C and D) did not ( $p = 0.035$ ).

### 3.4. Endocrinology Outcomes

Fifty-eight tumours were non-functional (72.5%) and 22 were functional pituitary tumours (27.5%).

During the evaluation of non-functional tumours before surgery, 13 patients had hypothyroidism, 12 had a complete anterior pituitary deficiency and one patient had hypoadrenalism. After the resection, 15 patients (18.75%) had a new hormonal deficit.

#### 3.4.1. GH-secreting adenomas (Table 5)

Amongst 17 patients with GH-secreting adenomas, 5 were microadenomas and 12 were macroadenomas, of which 5 had cavernous sinus

**Table 3**  
Rates of resection in adenomas with and without CSI\*

Adenomas	Number	GTR %	NTR %	STR %	PR %
Without CSI	61	76.2	18.9	3.3	1.6
With CSI	19	26.3	63.2	10.5	0

\* according radiographic evaluation (Knosp grade).

**Table 4**  
Extent of resection in 19 patients with CSI\*

Knosp Grade	GTR	NTR	STR	PR
2	4	3	1	
3	1	4	1	
4		5		

\* according radiographic evaluation.

**Table 5**  
Remission rates in patients with GH-secreting adenomas

GH Adenomas	Number	GTR	Remission EEA	Remission EEA + SAs *
Without CSI	12	9 (75%)	7 (58%)	8 (66.6%)
With CSI	5	3 (60%)	2 (40%)	4 (80%)
Total	17	12 (70.5%)	9 (52.9%)	12 (70.5%)

\* Somatostatin analogues

invasion. Remission was achieved in 58% in patients without CS invasion with EEA alone, and 40% in those with CS invasion. Adding medical treatment (somatostatin analogues), the remission achieved 70.5%.

Both cases in GH-secreting adenomas with cavernous sinus invasion were Knosp grade 2.

### 3.4.2. Prolactinomas

Of the four patients with prolactinomas, 2 were microadenomas (with intolerance to medical treatment) and 2 were macroadenomas (one with severe visual loss and one with failure treatment). Remission was achieved in both cases of microadenomas and in one with macroadenoma with EEA alone. Remission in one macroadenoma patient was obtained with surgery and further treatment with cabergoline; visual deficit returned to normal.

### 3.4.3. Thyrotrophic-secreting adenoma

One patient with thyrotrophic-secreting adenoma presented with a giant and irregular tumour. Remission was achieved with multimodality treatment including surgery on two different occasions (EEA + OZ approach), stereotactic radio-surgery and medical treatment.

### 3.5. Ophthalmologic outcomes

53 patients had visual deficits at the presentation. After the surgical procedure, 47 (88.6%) patients had improved visual function. Six patients with optic atrophy remained unchanged. No patient had worsened the visual function.

**Table 6**  
Postoperative complications

Complication	Number	%
Epistaxis	5	6.25
Mucocele	2	2.5
Anosmia	1	1.25
Sella Hematoma	3	3.75
CSF leak	10	12.5
- requiring re-exploration	5	6.25
New hormonal deficit	15	18.75
Permanent DI	3	3.75
Meningitis	1	1.25
Visual deterioration	0	0
Cranial nerve palsy*	1	1.25
ICA injury	0	0
Mortality	0	0

\* Temporary

### 3.6. Complications (Table 6)

The goals of surgery are restoration or preservation of vision, preservation of pituitary function, and maximal safe tumour removal; however some complications can be observed.

Complications have been divided into approach related (nasal and sinus complications) and resection related complications.

### 3.7. Approach related complications

#### 3.7.1. Epistaxis

Five patients (6.25%) had a moderate epistaxis between the days 3–7 after surgery; all of them required re-exploration of the nasal cavity to achieve haemostasis.

#### 3.7.2. Mucocele

Two patients (2.5%) developed sphenoid mucocele during the follow up. Both cases required surgery.

#### 3.7.3. Anosmia

One patient (1.25%) has permanent anosmia following reoperation for epistaxis.

### 3.8. Resection related complications

#### 3.8.1. Sella hematoma

Three hematomas (3.75%) in the sella region without clinical manifestations were found in the postoperative CT scan, however, the patients did not show the visual improvement that was expected and exploration and drainage was performed, achieving improvement in the immediate postoperative period.

#### 3.8.2. CSF leak

Ten patients (12.5%) had postoperative CSF leak. Five patients (6.25%) required further endoscopic exploration and repair plus lumbar drainage. In 5 of the 10 patients with CSF leak, we did not use the vascularized nasoseptal flap for reconstruction. It was incorporated into our technique beginning in 2013. GTR did not influence the percentage of CSF leak ( $p = 0.955$ ). In three patients the CSF leak closed with only lumbar drainage and two patients (2.5%) with delayed leak were treated with rest and acetazolamide.

#### 3.8.3. New hormonal deficiency (Table 7)

After EEA, 18.75% of the patients had a new hormonal deficit that required specific replacement therapy. Total resection was not a reason in the appearance of postoperative hormonal deficiency ( $p = 0.237$ ).

#### 3.8.4. Meningitis

One patient (1.25%) had meningitis related with CSF leak. The isolated pathogen was streptococcus viridans, which is a normal inhabitant or the oral, respiratory and gastrointestinal mucosa. The complication evolved satisfactorily after antibiotic treatment.

**Table 7**  
Post-operative hormonal deficits

Deficit	Number
Panhypopituitarism	1
Hypoadrenalism	8
Hypothyroidism	3
Permanent DI	3
Temporary DI	2

### 3.8.5. Cranial neuropathy

One patient had temporary sixth nerve palsy following the resection of tumour in the medial wall of the cavernous sinus. It was believed that excessive Surgiflo (Haemostatic Matrix Kit, Ethicon US, LLC) had been placed in the CS. The patients normal ocular movement returned 6 weeks after surgery.

### 3.8.6. Mortality and carotid artery injury

In the present series we do not have any mortality or injury to the internal carotid artery.

### 3.8.7. Follow-up

The follow-up was from 6 to 87 months. One patient failed the follow-up; in this case we performed a subtotal resection for a GH-secreting adenoma. One patient died 8 months after EEA due a non-neurological condition; and one patient presented with a high-grade glioma two years later. Two patients with subtotal resection were re-operated for size increase of the residual. Seven patients received stereotactic radiosurgery for residual lesions.

## 4. Discussion

The incorporation of endoscopy to the formal training of the neurosurgeon and the dissemination of the technique by world leaders, have made the EEA the choice in the management of pituitary adenomas. Although the microscopic technique is still used, endoscopy has proven similar in safety and efficacy [24], yet offers superiority in the angles of vision towards the suprasellar and the cavernous sinus regions.

Upon comparison, our outcomes are similar to previously reports.

### 4.1. Extent of resection

The percentage of gross total resection in non-functioning adenomas varies from 56% to 96% in different series [4,7,9]. Our results are similar when compared to the TRANSSPHER study that reports 80% and 83.7% of GTR in microscopic and endoscopic groups respectively [24]. Maximum tumour diameter > 40mm; nodular tumour extension through the diaphragm into the frontal lobe, temporal lobe, posterior fossa, or ventricle; and Knosp grades 3 to 4 were identified as independent STR predictors [25]. Cavernous sinus invasion is the most important factor that negatively affects the extension of resection. Paluzzi et al. [28] reported 35.4% and Cappabianca et al. [4] 36.8% of GTR in patients with CS compromise (26.3% in our series according radiographic criteria). Because we are a less experienced surgical team, we prefer to leave some residual tumour and avoid the risk of damage to the internal carotid artery or cranial nerves in the cavernous sinus.

In our experience, the resection was made more difficult when patients received medical treatment before surgery. We noted these tumours were harder and fibrotic, conditions that affect the extent of our resection.

Suprasellar extension, as long as it does not have multilobar configuration does not affect the degree of resection [7], condition that was confirmed in our results.

### 4.2. Functioning adenomas:

Surprising in our series we did not have ACTH secreting adenomas and there were only 4 cases of prolactinomas, which makes it impossible to compare with previous reports, (although we achieved 100% of biochemical cure in the latter group). We speculate that this is due a lack of accurate diagnosis in ACTH secreting adenomas. In prolactinomas cases, this may be because many endocrinologists in the city are treating these tumours medically.

In GH secreting adenomas, remission in all the patients is very difficult to obtain, even with GTR. CSI is again the main negative factor in this group. A 72% of remission with EEA alone in macroadenomas

without CSI was reported [28]. Although our percentage is lower (58%), the remission in the total series with complementary treatment is very similar (76% vs. 70.5%). Other microscopic or endoscopic series reported remission from 56% to 70.6% [3,7,9,27]. However, the long-term surgical remission rate appears to be significantly less than early remission rates. It is influenced by extend of resection, CSI, and preoperative and early postoperative GH and IGF-1 levels [2]. Multimodality treatment is used in these patients with somatostatin analogues and stereotactic radiosurgery.

### 4.3. Visual outcomes

The results in the present series are similar to previous reports [5,7,28]. Eighty-nine percent of patients improved. No patient worsened in the visual function, thanks to the endoscope's improved visualization of the suprasellar region. It is very important to inform the patient who has a clinical history of optical atrophy, that there is little or no possibility of improvement in vision after surgery.

### 4.4. Complications:

Complications from microscopic or endoscopic series have been reported in a range from 7 to 26.3% [4,7,9,18,31].

### 4.5. Complications related to approach

Nasal complications are reduced because the endoscopic technique avoids the septal incision and other parts of the nasal phase. Reports of nasal complications [1,9,28] include epistaxis (0.7–1.2%), sinusitis (0–0.9%) and anosmia (1%). In our series, we have high rates of epistaxis. Dehdashti et al. [7] reported low rates of epistaxis by meticulous cauterization of the posterior nasal branch of the sphenopalatine artery bilaterally, a step that we did not employ routinely. Anosmia was similar to the reports and was produced in an effort to achieve haemostasis after epistaxis. No cases of sinusitis occurred. Two cases (2.5%) of sphenoid mucocele were diagnosed in the MRI during the follow up, due an incomplete resection of the mucosa in the sphenoid sinus.

### 4.6. Complications related to resection

Pituitary insufficiency is reported in a range from 3 to 18% [7–9,12,28,31]. In this study 18.75% of patients had a new hormonal deficiency requiring specific replacement. In some cases, we had difficulty differentiating normal glandular tissue during the resection, which plays a role in our rate of anterior pituitary deficiency. A 28.4% of this complication was reported in the microscopic group in the most recently prospective multicentre study [24].

Postoperative hematoma has been reported in a very low rate from 0.4% to 2.7% [7,9,13,28] producing visual deterioration with the need for urgent evacuation. In the present series we had three patients with sella hematoma, however, these were discovered in the postoperative CT scan, without presenting visual deficits.

CSF leak is a big concern for endoscopic surgeons. The introduction of the vascularized nasoseptal flap for reconstruction greatly decreases the rates of CSF leak [15]. Reduction from 11.5 to 2.9% after its use was reported in 2013 [28]. In this report, CSF leak reflected the number of patients requiring further endoscopic repair. Our exploration percentage to control CSF leak was 6.25%. The use of nasoseptal flap leads us to reduce the CSF leak to 5%. Although the technique for creation of the vascular pedicle nasoseptal flap for reconstruction was described in 2006, we started using the technique in 2013, after learning about it in a training course.

Serious complications such as injury to the internal carotid artery, cranial neuropathy or mortality are rare, with percentages < 1% [5,7,9,13,28]. We did not experience these complications because we prefer to leave some residual tumour in the cavernous sinus, since after

STR the need for intervention at 10 years is 20% and a period of observation may be warranted [10]. Also, SRS plays a significant role in the treatment of pituitary adenomas, achieving good growth control [26].

Although on average we had a slightly higher percentage of complications, none was significant in the final result. We believe that this is due to our learning curve and improving techniques when comparing our results with those reported by the leaders in the world.

#### 4.7. Limitations of this study

The most important limitation of this study is the number of cases. Coming from a small country where several endocrinologists are not yet familiar with the surgical resolution of pituitary adenomas could cause this. Another limitation is the retrospective nature of the study.

#### 5. Conclusions:

The results of different reports around the world ratify endoscopic endonasal surgery as the choice in pituitary tumours; in many centres, this technique is now routinely used. A multidisciplinary management is required for the adequate treatment of pituitary adenomas. With good surgical training, the EEA is safe and effective. Our results are similar compared with those reported in previous series of microscopic or endoscopic approaches. A learning curve is essential to reduce the complications related to the approach.

#### CRedit authorship contribution statement

**Sebastian Lopez:** Conceptualization, Methodology, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Project administration. **Miguel Jerves:** Conceptualization, Methodology, Investigation. **Franklin Santillan:** Methodology, Investigation, Writing - original draft. **Gabriela Jimenez:** Investigation, Resources. **Maria Augusta Astudillo:** Investigation, Resources. **Fabian Cardenas:** Investigation, Resources. **Hernan Aguirre:** Methodology, Software, Validation, Formal analysis.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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