Binostril Endoscopic Trans-Sphenoidal Approach for Pituitary Adenomas

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Abstract

Introduction: Pituitary adenomas are a common intracranial tumors, that account for 15% of all intracranial neoplasms, they arise from the sella turcica, and grow vertically toward the supra sellar cisterns. They either functioning tumors which secrete hormones or non functioning tumors. Surgical treatment is considered a second option in treating such pathology in functioning adenomas after failure of medical treatment, however in non functioning adenomas they gain a large size leading to pressure symptoms, in such cases surgical intervention is considered as the first treatment option.

Material and Methods: Twenty six patients submitted to endonasal endoscopic removal of pituitary adenomas with a follow-up from 6 to 24 months, all patients were investigated pre-operatively by brain magnetic resonance imaging as well as computed tomography, also hormonal analysis for all pituitary hormones, full visual assessment. Patients with prolactin hypersecretion were subjected to surgery after failure of medical treatment, follow-up MRI brain and sella with contrast was done in all cases in the first post-operative day also 3 months for full evaluation.

Results: Ten women and sixteen men, age range 29-65 years. 24 patients were harboring macroadenoma while 2 patients had microadenoma in the pre-operative scans. Hormonal assay revealed 15 non-secreting adenomas, 6 growth hormone hypersecretion, and 4 patients has hyperprolactinemia, one case of ACTH secreting adenoma. Visual manifestations were the main presenting symptoms followed by headache. Three patients developed intraoperative Cerebrospinal Fluid (CSF) leaks that was treated by fat graft and tissue glue, five patients developed diabetes insipidus it was transient in four and remained persistent in one patient. While gross total excision was achieved in 21 patient.

Conclusion: The binostiral endoscopic endonasal transsphenoidal approach for pituitary adenomas is effective with low surgical morbidity that it provides resection of pituitary tumors under excellent visualization and should be used on routine basis to resect lesions of the pituitary gland.

Key Words: Pituitary adenoma – Endoscopy – Trans-sphenoid.

Trans-sphenoidal surgery for pituitary adenomas was firstly invented by Herman Schloffer more than 100 years ago [3]. It was then evolved over time from trans-sphenoidal surgery by microscope into endoscope-assisted microscopic surgery, and nowadays has progressed to pure endoscopic endonasal surgery [4,5].

The endoscopic endonasal transsphenoidal approach through the bilateral nostrils was evaluated for the treatment of pituitary adenoma. The surgical approach is through the bilateral nostrils via min-
imal or wide dissection of the septal mucosa, depending on the degree of tumor extension. After anterior sphenoidotomy, the endoscope is fixed in one nostril and required instrumentation is inserted in either nostril.

Endoscopic approach provides better visualisation and excellent access to tumors at the corners and at the suprasellar compartment [6,7].

**Patients and Methods**

**Clinical assessments:**
A total of 26 patients with pituitary adenomas were admitted to Neurosurgery Department Menofiya University Hospital, all were operated via endoscopic endonasal technique in the period between February 2012 to March 2015.

Clinical presentation were collected retrospectively from patient files laboratory investigation.

Hormonal profile including serum prolactin (PRL), growth hormone (GH), insulin like growth factor1 (IGF 1) in patients with acromegalic features, serum ACTH, routine laboratory work up was done for all patients pre-operatively and first day post-operatively and after 3 month from the surgery.

**Radiological assessment:**
- All patients had contrast CT, Gadolinium MRI brain and sella post operative Gadolinium MRI was done at 1st day post-operatively and after three months.

Patients were classified according to Hardy, modified Hardy and Knosp classification according to the degree of extension inside the sella, suprasellar extension and degree of cavernous sinus invasion respectively (Table 1).

**Hardy’s classification:**
- **Microadenomas:**
  - Grades 0 and I.
- **Macroadenomas:**
  - Grades II to IV.

**Grade 0:** Intrapituitary microadenoma with normal sellar floor.
**Grade I:** Normal-sized sella with asymmetric floor.
**Grade II:** Enlarged sella with an intact floor.
**Grade III:** Localized erosion of sellar floor.
**Grade IV:** Diffuse destruction of floor.

**Modified Hardy Wilson classification:**
- **Type A:** Tumor bulges into the chiasmatic cistern.
- **Type B:** Tumor reaches the floor of the 3rd ventricle.
- **Type C:** Tumor is more voluminous with extension into the 3rd ventricle up to the foramen of Monro.
- **Type D:** Tumor extends into temporal or frontal fossa.
- **Type E:** Extradural spread (extension into or out of the cavernous sinus).

**Knosp classification system:**
- **Grade 0:** No cavernous sinus involvement.
- **Grade 1:** The tumor pushes into the medial wall of the cavernous sinus, but it doesn’t grow beyond a hypothetical line extending between the center of two segments of the internal carotid artery.
- **Grade 2:** The tumor pushes into the medial wall of the cavernous sinus, but it doesn’t grow beyond a hypothetical line extending between the lateral wall of two segments of the internal carotid artery.
- **Grade 3:** The tumor extends laterally to the internal carotid artery within the cavernous sinus.
- **Grade 4:** Total encasement of the intracavernous carotid exclusion criteria.

Patients with prolactinomas were only indicated if they were resistant or intolerance to medical treatment patients with sphenoid sinus.

**Surgical methods:**
- The nose is anesthetized with a cocktail of 4% lidocaine hydrochloride with 1:100,000 epinephrine on cottonoid pledgets and then 1% lidocaine is infiltrated bilaterally into the mucosa of the bony septum.

- The instruments including 0°, 30°, wide-angle lens, 4-mm diameter rigid endoscopes (Karl Storz, Germany), endoscopic surgical instruments (Karl Storz, Germany).

**Procedure:** Both nostrils were used starting from the right nostril, middle turbinate were mobilized medially then displaced laterally if it was
found to be large and obstructing the view it was
removed to gain more operative space. The right
nostril is used to introduce the endoscope and left
nostril used to introduce the instruments.

Mucosal flap dissection was used depending
on tumor extension and the need for sellar recon-
struction with a mucosal flap. C-shaped incision
was placed in the bilateral septal mucosa around
the ostium to treat most pituitary tumors, followed
by enlargement of the bilateral ostia. The mucosal
flap was reflected and used to repair the sellar
floor in pediculate fashion if intraoperative CSF
occurs posterior part of the cartilaginous sputum
is opened to visualize the anterior wall of the
sphenoid. The mucosa over the anterior wall of
the sphenoid sinus was cutarized and displaced
laterally.

The anterior wall of the sphenoid sinus is re-
moved using a high speed drill. After the sphenoid
sinus was opened, the mucosa lining the sphenoid
sinus is resected. Sellar dura was fully exposed
according to the size and location of the tumor.
The two cases of microadenomas underwent ext-
racapsular dissection while macroadenomas were
resected piecemeally (intrasellar firstly starting
from the posterior part then anterior, then supra-
sellar, finally, explore the bilateral medial wall of
cavernous sinus and remove the residual tumor
invading into the cavernous sinus if possible using
the 30 degrees optics the sella then packed by fat
graft harvested from the subcutaneous periumbilical
region then piece of gel foam and then nasal back
through the right nostril.

Mucosal flap was raised in 4 cases where intra-
operative CSF leak was noticed intra operatively
to reconstruct the sellar floor.

**Post-operative radiological evaluation:**

First post-operative day MRI scan sella with
contrast was done in all cases to check for the
extent of surgical resection. All the patients en-
rolled underwent a total endocrine evaluation on
the first post-operative day and 3 months. Following
surgery 3 months, 6 months and each year after
discharge. MRI scan was advised each time since
the second follow-up (the third post-operative
month). The criteria for endocrinological remission
of GH-secreting adenoma were: GH level <0.4ug/L
or random GH level <1ug/L and IGF-1 level was
at normal range according to the age and sex
simultaneously. The normal range for PRL was
<22.80ug/L for male, and <30.74ug/L for female.

**Histological evaluation:**

All tumour samples were examined by one
pathologist, histopathological examination, immu-
nohistochemistry staining was used in all samples.

**Statistical evaluation:** Chi-square test and Fish-
er’s exact test were used. A $p$-value <0.05 was
considered significant. Statistical analyses were
performed using SPSS software (Version 17.0).

**Results**

A total of 26 patients with pituitary adenomas
were included in this study. 16 males and 10 fe-
males, age ranged from 29 to 64 years with mean
age 39±7.2 years. The main clinical presentation
were headache in 20 (76.9%) patients followed by
impairment of version and visual field defect in
18 (69.2%) patients, menstrual disorder/ galactor-
rhea in 3 (11.5%) patients, acromegalic features 4
(15.3%) patients, male sexual dysfunction in one
(3.8%) patient, central obesity and chushenoid
features in one (3.8%) patient (Table 1).

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender:</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16 (61.5% )</td>
</tr>
<tr>
<td>Female</td>
<td>10 (38.5% )</td>
</tr>
<tr>
<td>Presenting symptoms:</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>20 (76.9% )</td>
</tr>
<tr>
<td>Visual problems</td>
<td>18 (69.2% )</td>
</tr>
<tr>
<td>Amenorrhea/galactorrhea</td>
<td>3 (23.1% )</td>
</tr>
<tr>
<td>Acromegalic features</td>
<td>5 (19.2% )</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>1 (3.8% )</td>
</tr>
</tbody>
</table>

Pre-operative sellar coronary CT and MR ex-
aminations were performed in all patients.

According to Hardy classification was utilized
according to the size of tumor: Grade 0 no cases,
Grade I in two patients, Grade II thirteen patients,
Grade III in six patients, Grade IV in five patients.

According to modified Hardy classification:
Type A in eleven patients, Type B in six patients,
Type C in one patients.

According to the Knosp grading The degree of
invasion to the cavernous sinus: Grade 0 in 23
patients, Grade I two patients, Grade II in one
patient.

18 cases (69.2%) were invasive adenomas and
8 cases (30.8%) were non-invasive adenomas
(Table 2).
Table (2): Radiological criteria of 26 patients with pituitary adenomas.

<table>
<thead>
<tr>
<th>Radiological grading</th>
<th>Number of patients (%)</th>
</tr>
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<tbody>
<tr>
<td><strong>Hardy grade:</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>2 (7.7%)</td>
</tr>
<tr>
<td>Grade I</td>
<td>13 (50%)</td>
</tr>
<tr>
<td>Grade II</td>
<td>6 (23.1%)</td>
</tr>
<tr>
<td>Grade IV</td>
<td>5 (38.5%)</td>
</tr>
<tr>
<td><strong>Modified Hardy classification:</strong></td>
<td></td>
</tr>
<tr>
<td>Type A</td>
<td>11 (94.2%)</td>
</tr>
<tr>
<td>Type B</td>
<td>6 (23.1%)</td>
</tr>
<tr>
<td>Type C</td>
<td>1 (7.7%)</td>
</tr>
<tr>
<td><strong>Knosp grading:</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>23 (88.5%)</td>
</tr>
<tr>
<td>Grade I</td>
<td>2 (7.7%)</td>
</tr>
<tr>
<td>Grade II</td>
<td>1 (3.8%)</td>
</tr>
<tr>
<td><strong>Invasiveness:</strong></td>
<td></td>
</tr>
<tr>
<td>Invasive</td>
<td>18 (69.2%)</td>
</tr>
<tr>
<td>Non-invasive</td>
<td>8 (30.8%)</td>
</tr>
</tbody>
</table>

Laboratory investigations revealed hormonal hypersecretion in 11 patients (hyperprolactinemia in 9 patients, IGF 1 increase in 6 patients, ACTH in one patient), while 15 patients had no laboratory manifestation of hormone hypersecretion.

According to the immediate post-operative radiological evaluation, Growth Total Removal (GTR) was achieved in total of 21 patients, 5 patients had residual tumors, two of them were taken back to the theater next day post-operative to resect the residual tumor, two patients with cavernous sinus invasion ,one patients refused second look surgery and preferred the wait and see policy.

According to immunohistochmisterical examination of the tumor biopsy collected, it revealed Null cell adenoma in 15 cases, GH-secreting adenomas in 5 cases, prolactin secreting adenoma in 4 cases, mixed GH- prolactin secreting adenoma in one case and ACTH-secreting adenomas in one case.

Three patients had intra operative CSF leak, which was managed intra operatively with septal flap reconstruction of the sellar floor, together with fibrin glue and fat graft harvested from the para umbilical region and lumbar drain for 5 days.

Diabetes insipidus was noticed in total of 5 patients, during the post-operative period, however it was transient in 4 patients and remain permanent in one patient.

The relation between the clinical & histological diagnosis and pre-operative radiological grading is shown in Table (3), the invasive adenomas were found in all cases with non functioning adenomas, while 1 of 4 prolactinomas, and 2of 5 GH-secreting adenomas.

### Table (3): Relation between clinical & histological diagnosis and radiological grading in 26 patients with pituitary adenomas.

<table>
<thead>
<tr>
<th>Histological type</th>
<th>Invasive n (%)</th>
<th>Non-invasive n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non functioning adenoma</td>
<td>15 (57.7%)</td>
<td>3 (11.5%)</td>
</tr>
<tr>
<td>Prolactionma (PRL)</td>
<td>1 (3.8%)</td>
<td>3 (11.5%)</td>
</tr>
<tr>
<td>GH-adenoma</td>
<td>2 (7.7%)</td>
<td>3 (11.5%)</td>
</tr>
<tr>
<td>Mixed GH &amp; PRL adenoma</td>
<td>1 (3.8%)</td>
<td>1 (3.8%)</td>
</tr>
<tr>
<td>ACTH adenoma</td>
<td>–</td>
<td>1 (3.8%)</td>
</tr>
</tbody>
</table>

### Table (4): Factors affecting the extent of surgical removal by endoscopic surgery of 26 patient with pituitary adenomas.

<table>
<thead>
<tr>
<th>Tumor size:</th>
<th>Extent of surgical resection</th>
<th>Test of significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hardy Grade I &amp; II</td>
<td>N=15 Total resection n (%)</td>
<td>Subtotal resection n (%)</td>
</tr>
<tr>
<td>Hardy Grade III &amp; IV</td>
<td>N=11</td>
<td>8 (72.7%)</td>
</tr>
<tr>
<td>Endocrine type:</td>
<td>Non functioning adenoma</td>
<td>N=15</td>
</tr>
<tr>
<td>Functioning adenoma</td>
<td>N=11</td>
<td>8 (72.7%)</td>
</tr>
<tr>
<td>Invasiveness:</td>
<td>Invasive</td>
<td>N=18</td>
</tr>
<tr>
<td>Non invasive</td>
<td>N=8</td>
<td>8 (100%)</td>
</tr>
<tr>
<td>Knosp grade:</td>
<td>Grade 0</td>
<td>N=23</td>
</tr>
<tr>
<td>Grade I, II, III, IV</td>
<td>N=3</td>
<td>1 (33.3 %)</td>
</tr>
</tbody>
</table>

FE: Fisher exact test.
We analyzed the factors associated with extent of surgical removal of tumors, according to tumors size. 14 of 15 tumors with Hardy Grade I & II had total tumor excision while 8 of 11 tumors Hardy Grade III & IV had total tumor excision, according to endocrinological activity. 13 of 15 cases with non-functioning adenoma had total removal, while 8 of 11 cases with functioning adenoma had total removal, according to the invasiveness nature of the tumor. All tumors who were classified non-invasive at the pre-operative imaging had total removal while 13 of 18 cases, according to degree of cavernous sinus invasion. 20 of 23 patients with Kosp Grade 0 had total excision, while 1 of 3 with Kosp Grade I, II, III, IV had total excision.
Discussion

Pituitary adenomas are considered as histologically benign nature. However, some can grow inside the sella with expansion of the sellar boundaries and this may be reflected clinically by headache, moreover compression over the normal pituitary gland may be presented by manifestation of hypopituitarism, or it can grow into giant and invasive tumors extending beyond the boundaries of the sella, invasive pituitary adenomas is a radiological discription of pituitary adenomas that infiltrates or destroys the normal confines of pituitary gland, including diaphragma sellae, cavernous sinus, or basal dura. The direction of spread depends on the pathway of least resistance, with upward extension into the suprasellar space being the most common and this is responsible for the clinical presentations of visual deterioration due to pressure on the optic pathways or lateral expansion. In this small series of pituitary cases, invasive tumors by this definition was encountered in 18 patients 69.8% out of this cavernous sinus invasion was only seen in three patients.

Pituitary adenomas with cavernous sinus invasion often present clinical symptoms of pituitary adenoma and cavernous sinus invasion. Chronic headache, visual disturbances, and hyper-endocrine are common clinical symptoms. If the tumor invades intra-cavernous nerves or vessels, it would present the cavernous sinus syndrome including oculo-motor, trochlear and abducent nerve paralysis, and trigeminal neuralgia. In our data, although the cavernous sinus invasion was confirmed in three patients, none of them presented cavernous sinus syndrome. The consequences of cavernous sinus invasion caused by pituitary adenomas are clinically important because the surgery is usually more difficult and less efficient. The invasion increases the incidence of intra-operative injury to intracavernous ICA and cranial nerves.

Schloffer et al., were the first to report the transsphenoidal approach in a sella tumor in 1907. It was Cushing et al., who abandoned external incisions and popularized the transsphenoidal transsphenoidal technique. In the 1960s, Hardy perfected Cushing’s approach with the introduction of the operative microscope. The traditional transseptal/translabial approach has long been considered as the standard approach because it is associated with minimal morbidity and mortality.

In recent years, with the development of endoscopic instruments and techniques, Jankowski proposed a fully endoscopic approach to pituitary surgery in 1992. Currently, endoscopic transsphenoidal pituitary surgery has become a preferred alternative option because of its advantages of improved visualization and minimal invasiveness, which allows surgeons to gain access to central skull base lesions.

With the development of endoence optical system and surgical instrument, especially the use of wide-angled panoramic endoscope, the operators can have clear visualization of parasellar region and various anatomic corners. Compared with the transcranial and microscopic transsphenoidal approaches, endoscopic transsphenoidal approach has close-up inner view when removing the tumor. Entoectad aspiration or curette in the tumor cavity could reduce bleeding and render minute details at the tumor removal site, allowing clear discrimination of the border of tumor and avoiding injury to the cavernous sinus.

The endoscopic technique appears to provide a higher rate of Growth Total Resection (GTR) compared with microscopic resection. The results from Gao et al., [9] in their meta-analysis showed that the rate of GTR was significantly higher in the endoscopic group than in the microscopic group (71.8% versus 58.0%). The degree of gross total removal for tumors with suprasellar or parasellar extension and without cavernous sinus involvement was 96% and for intrasellar lesions was 98%.

In the series of Dehdashti et al., [10] gross total removal was achieved in 79.3% of the cases after a median follow-up of 61.5 months in series reported by Gondim et al., [11] in their series of 228 pituitary adenomas. The remission results for patients with nonfunctioning adenomas was 83% and for functioning adenomas were 76.3% (70.6% for GH hormone-secreting, 85.3% for prolactin hormone-secreting, 71.4% for ACTH hormone-secreting, 85.7% for FSH-LH hormone-secreting and 100% for TSH hormone-secreting), with no recurrence at the time of the last follow-up. In this series growth total removal was achieved in 13 out of 15 (86.7%) patients with non functioning adenomas, while growth total removal was achieved in 8 out of 11 (72.7%) patient with functioning adenomas which are comparable to the other reported series.

In Gao et al., [9] meta-analysis most of invasive macroadenomas were difficult to be totally removed i.e. Hardy stage III-IV as tumor grows expansively, tumors invading laterally (cavernous sinus etc.) are harder to be removed than those invading vertically (suprasellar, sphenoid sinus, clivus etc.).
Univariate analysis of the clinical data showed that total removal rate was related to tumor volume \((p=0.006)\), reoperation \((p=0.011)\), learning curve \((p=0.009)\) and much closer to tumor invasiveness \((p<0.001)\). We statistically correlated factors associated with total surgical removal we found that tumor size and invasive nature of the tumor were most significant predictive factors, we have three case of cavernous sinus invasion, two of them had residual tumors at post-operative imaging as it need good experience and familiarity of the surgeon with the anatomy of this region together with intra-operative Doppler to avoid injury of the carotid artery.

Using our procedure, tumor removal exceeded 80% in 21 of 26 pituitary adenomas. Although others reported higher removal rates, the difference may be attributable to lack of experience especially with large infiltrative tumors with lateral extension into the cavernous sinus.

Endoscopic procedures are associated with complications such as CSF leakage (0.0-28.0%), anterior pituitary insufficiency (12.0-13.6%), and long-term diabetes insipidus (2.0-7.0%), post-operative visual worsening, intracranial hemorrhage, intra cranial infection, mortality. Gondim JA et al., [11] in total of 228 series post-operative complications were present in 35 (13.9%) cases. The most frequent complications were temporary and permanent diabetes insipidus (six and two cases, respectively), syndrome of inappropriate antidiuretic hormone secretion (two cases) and CSF leaks (eight cases). There was no death related to the procedure in this series, [10] in our series three patients developed intra operative CSF leak intra-operatively, it was repaired using septal flap reconstruction of the sellar floor together with tissue glue, five patients developed post-operative diabetes insipidus with remained permanent in only one patient.

Zhou et al., [12] in their series of 492 pituitary adenomas via endoscopic approach intraoperative CSF leakage occurred in 86 cases (17.5%). On univariate analysis, there were three factors associated with an increased intraoperative CSF leak rate, repeat surgery (repeat 30.0% vs. primary 16.4%; \(p=0.033\)), consistency of the adenoma (tenacious, 27.3% vs. soft, 13.5%; \(p=0.000\)), tumor size \((22.0\pm 9.7\text{mm vs. }25.4\pm 11.5\text{mm}; p=0.007)\). However, on multivariate analysis, only tumor consistency \((p=0.001; \text{OR}=2.379)\) and tumor size \((p=0.026; \text{OR}=1.032)\) were independently associated with intraoperative CSF leaks.

The primary complication for the majority of patients undergoing pituitary surgery is CSF leak. The currently accepted view is that the success of reconstructive techniques following dissection should be a major determinant of post-operative CSF leak. Endoscopy appears to have a huge advantage in reconstruction because it improves visualization. The main reason for this similarity may be that the improved exposure during endoscopic surgery would encourage the surgeons to extend the limits of their operation more aggressively, which may offset the minimally invasive nature of endoscopic resections and increase the rate of post-operative CSF leak [13].

Intracranial hemorrhage is one of the most serious complications of endoscopic endonasal surgery for two reasons, residual tumor bleeding, if together with sellar diaphragm rupture, can penetrate to the subarachnoid space or ventricles, and the excessive collapse of sellar diaphragm may rupture the perforator arteries which adhere to the sellar diaphragm and cause acute bleeding. The former bleeds slowly and can be confirmed by post-operative CT scan. The latter may cause massive hemorrhage and progresses quickly, even lead to death intra-operatively, which makes it hard to handle [2].

Recommendations to decrease complication during endoscopic pituitary surgery at the beginning of endoscopic surgery, problems like inadaptation to the endoscopic visualization, the narrow operational space or lack of endoscopic instruments usually showed up. It takes patience and perseverance for neurosurgeons to overcome difficulties, familiarize with and adapt to the endoscopic surgery. Thus, it is recommended to the beginners that operating on those who have a smaller tumor and bigger nasal cavity at the very start. Removal of partial middle turbinate to gain more operational space is also a good choice. Of course, with the company of an experienced ENT doctor [12].

Our experience with the bilateral endonasal approach suggests that after dissection of the mucosa and opening of the anterior wall of the sphenoid sinus, the surgical field is similar to that yielded by the unilateral approach. In addition, instrument manipulation is easier, possibly because the nostril is flexible and there is no interference from a nasal speculum. The bilateral approach enhances surgical effectiveness because the combined action of more than 2 instruments facilitates bleeding control and lesion removal, and the contralateral working angle can be increased by changing to the other nostril.
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References


