Evidence of improved surgical outcome following endoscopy for nonfunctioning pituitary adenoma removal

Personal experience and review of the literature

MAHMOUD MESSERER, M.D.,1 JUAN CARLOS DE BATTISTA, M.D.,1 GÉRALD RAVEROT, M.D.,
PH.D.,1 SEBOUGH KASSIS, M.D.,1 JULIE DUBOUG, M.D.,3 VERONIQUE LARAS, M.D.,4
JACQUELINE TROUILLAS, M.D., PH.D.,5 GILLES PERRIN, M.D.,6 AND EMMANUEL JOUANNEAU, M.D., PH.D.7

1Département de Neurochirurgie A, Hôpital Neurologique Pierre Wertheimer, Groupement Hospitalier Est,
Hospices Civils de Lyon; 2Institut National de la Santé et de la Recherche Médicale U1028, CNRS UMR5292,
Faculté de Médecine Lyon Est, Université de Lyon I, Fédération d’Endocrinologie, Groupement Hospitalier Est,
Hospices Civils de Lyon; 3Université de Lyon I, Centre d’Investigation Clinique CIC201,
Hôpital Louis Pradel, Groupement Hospitalier Est, Hospices Civils de Lyon; 4Département de Radiologie,
Centre Hospitalier Lyon Sud, Hospices Civils de Lyon; 5Institut National de la Santé et de la Recherche Médicale
U1028, CNRS UMR5292, Faculté de Médecine Lyon Est, Université de Lyon I, Département d’Histologie et
d’Embryologie Moléculaire, Centre de Pathologie Est, Groupement Hospitalier Est, Hospices Civils de Lyon;
6Faculté de Médecine Lyon Est, Université de Lyon I, Département de Neurochirurgie C,
Hôpital Neurologique Pierre Wertheimer, Groupement Hospitalier Est, Hospices Civils de Lyon; and 7Institut
National de la Santé et de la Recherche Médicale U1028, CNRS UMR5292, Faculté de Médecine Lyon Sud,
Université de Lyon I, Département de Neurochirurgie A, Hôpital Neurologique Pierre Wertheimer,
Groupement Hospitalier Est, Hospices Civils de Lyon, Bron, France

Object. Because of their size and lateral extension, total removal of nonfunctioning pituitary adenomas (NFPAs)
remains a challenge and postoperative tumor remnants are frequent. Endoscopy has improved the surgeon’s view; however,
its superiority in terms of surgical outcome remains undetermined. The authors’ aim in this study was to compare
the clinical results and morbidity between microscopic and endoscopic techniques in 164 patients with NFPAs.

Methods. Tumoral (3D MR imaging), endocrinological, and ophthalmological results and morbidity were com-
pared between 2 groups of 82 patients with newly diagnosed NFPAs surgically treated via either a sublabial micro-
scopic approach (Group B) or a fully endonasal endoscopic technique (Group A).

Results. The groups showed no difference in terms of clinical features, tumor size, or cavernous sinus invasion (p
> 0.05). One year postoperatively, the quality of resection was significantly improved in Group A (gross-total removal
[GTR]: 74% vs 50% in Group B, p = 0.002) with greater control of lateral extension (Knosp Grade 2: GTR 88.2%
vs 47.8% in Group B, p = 0.02; Knosp Grade 3: 67.9% vs 16.7% in Group B, p < 0.001) and suprasellar extension
(tumor height 20–30 mm: GTR 76% vs 53% in Group B, p = 0.01). Endocrinological outcome in patients with a
partial deficiency in anterior pituitary function preoperatively was significantly better in Group A (improvement 56%
vs 25% in Group B, stabilization 22% vs 46%, and aggravation 22% vs 29%; p = 0.01). Among the ophthalmologi-
cally symptomatic patients, 100% from Group A improved compared with 93% in Group B (p = 0.35). Lastly, no
significant difference was found regarding morbidity. These data were supported by the literature in which the GTR
rate is consistently higher for endoscopy compared with microscopy.

Conclusions. In this large series of patients with NFPAs, endoscopy improved the quality of resection and endo-
crinological outcome. Larger studies focusing on the impact of these promising results on the long-term recurrence
of NFPAs are warranted. (DOI: 10.3171/2011.1.FOCUS10308)

Key Words • endoscopy • minimally invasive surgery • nonfunctioning pituitary adenoma • transsphenoidal surgery

Since the introduction of operative microscopy and intraoperative fluoroscopy by Guiot et al.16 and
Hardy18 in the 1960s, microsurgery via a transsphe-

Abbreviations used in this paper: ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; GH = growth hor-
mone; GTR = gross-total resection; ICA = internal carotid artery; LH = luteinizing hormone; NFP = nonfunctioning pituitary adenoma; PRL = prolactin; TSH = thyroid-stimulating hormone.
1990s, endoscopy marked an important milestone for pituitary or skull base surgery and was widely promoted in particular by Cappabianca et al. and Jho and Carrau. While the endoscopic endonasal approach is becoming the technique of choice for pituitary surgery, improvements with regard to surgical outcome remain undetermined.

Immunonegative, gonadotropin, and silent adenomas are grouped under the name of NFPA since they have no specific clinical symptoms. Often diagnosed late as macroadenomas, they remain a challenge to neurosurgeons given the frequent occurrence of residual tumor postoperatively. Since endoscopy permits better visualization of the operative site, we predicted that this approach would in turn permit better resection. To test this hypothesis, we compared our data for 164 NFPA from 2 consecutive series surgically treated by the same surgeons—82 via the microscopic approach and 82 via a fully endoscopic approach—and reviewed the literature available on this topic.

Methods

Study Population

Inclusion Criteria. Between 2006 and 2009, 350 patients bearing pituitary adenomas underwent consecutive surgical treatment via a purely endonasal endoscopic approach by the same senior surgeon (E.J.) in our department. Newly diagnosed NFPA were found in 82 of the patients (Group A). To assess endoscopic versus microscopic surgical techniques we compared Group A with the last 82 consecutive patients with newly diagnosed NFPA treated in the preceding year via a sublabial microsurgical approach (Group B) undertaken by the same senior pituitary surgeon (E.J., > 300 patients treated microscopically) or another expert pituitary surgeon (G.P., > 1000 patients treated microscopically).

Exclusion Criteria. Patients previously treated with surgery or radiation, younger than 18 years of age, or with < 6 months of follow-up at the time of the study were excluded from the analysis.

Surgical Procedure

Group A: Endoscopic Approach. Patients in Group A underwent pure endonasal endoscopic transsphenoidal surgery with a 4-mm rigid endoscope (Karl Storz) and an intraoperative MR imaging neuronavigation system (Medtronic) as previously described. Briefly, which side of the nasal cavity to use was determined by the nasal anatomy (septal deviation and meagaturbinate), lateral extension (contralateral approach to a lateral extension), and size of the tumor (bilateral for large tumors). A unilateral approach was used in most cases, except for large tumors. The entire endonasal procedure until the opening of the sellar floor was performed with a hand-held, short 0° endoscope (4 mm, 18 cm). The superior and middle turbinates were identified and gently pushed aside laterally. Mucosa from the sphenoideal ostium to the choana at the base of the vomer was coagulated and thereafter opened up, pushing away the vomer until the contralateral ostium appeared. A large sphenoidotomy was performed, and the bone of the sella turcica was removed from one cavernous sinus to the other and from the anterior skull base to the clivus. After opening the dura mater, a long 0° endoscope (4 mm, 24 cm) fixed on a table-mounted endoscope holder was introduced into the nostril allowing both hands for tumor dissection and removal. Adenomas were removed using a piecemeal technique similar to that applied in microscopic surgery. At the end of the procedure, the sellar and suprasellar regions were explored using 0°, 30°, and rarely 45° endoscopes pushed up through the sella turcica. At the end of the procedure, jugular compression was applied to detect any CSF fistula before closing. The closure technique did not differ from the one used during microscopic surgery; bioabsorbable dura mater was placed in the extradural plane with fibrin glue if no CSF leakage occurred and we used autologous material such as fat or fascia lata with fibrin glue and CSF lumbar drainage or puncture in the event of a fistula. No nasal packing was used with the endoscopic technique.

Group B: Microscopic Approach. Patients in Group B underwent the traditional sublabial transseptal transphenoidal surgery described by Guiot et al. in 1959 and Hardy in 1969. Briefly, a short incision was made in the superior gingival sulcus, and the cartilaginous septum was pushed away to the left, allowing placement of a nasal speculum. The sphenoid was opened up and the speculum was pushed inside. Under microscopic visualization, sellar opening, tumor removal, and sellar closure techniques were performed as described above for the endoscopic technique. At the end of the surgery, the mucosa was closed with absorbable sutures, and bilateral nasal packing was placed in each nostril for 24 hours.

Neuroimaging Evaluation

Before surgery, the imaging protocol included systematic 3D T1-weighted sequences with and without contrast injection and a 3D T2 sequence, plus an additional neuronavigation sequence using 1.5-T MR imaging (Siemens) for Group A. Tumor volume (height × length × width), tumor height, and cavernous sinus invasion were defined using coronal T2 and 3D T1-weighted MR imaging with and without contrast injection, with a special note for the latter 2 parameters considered as important factors determining surgical failure. For cavernous sinus invasion, the Knosp classification was used. According to Knosp et al., grade 0–1 tumors are considered noninvasive to the cavernous sinus (do not cross the cross-sectional centers of the intra- and supracavernous ICA); most Grade 2 lesions (extending beyond the intercarotid line but not beyond or tangent to the lateral aspects of the intra- and supracavernous ICA) and Grade 3 tumors (extending beyond the tangent on the lateral aspects of the intra- and supracavernous ICA) are considered invasive; and Grade 4 lesions (surrounding the ICA) clearly invade the cavernous sinus. If the grading was different between the 2 cavernous sinuses for any patient, the tumor was classified according to the higher grade. In 1 case in which MR imaging was not
Endoscopy improves the surgical outcome of NFPA

feasible for health reasons (pacemaker), a CT scan with 3D reconstruction was obtained.

At 3, 6, and 12 months following surgery and once per year thereafter, all patients surgically treated for pituitary adenomas at our center underwent postoperative control MR imaging with the same sequences as those performed preoperatively (except for neuronavigation). As the goal of this study was to evaluate the quality of tumor removal with respect to the technique applied, we used the 12-month postoperative MR imaging study for analysis to avoid any artifacts. The quality of resection, as judged by the 2 senior pituitary surgeons (E.J. and G.P.) and an independent neuroradiologist (V.L.), was classified as total or subtotal (classified as subtotal in cases of doubt). Any remaining residue was classified in terms of its location (suprasellar, parasellar, or intracavernous) and eventually its compressive effect on the optic chiasma.

**Endocrinological Evaluation**

Before and after surgery, all patients were assessed with static and dynamic endocrinological tests to globally evaluate anterior pituitary function.

After surgery, patients’ conditions were classified as having improved or worsened when one sector of pituitary function had been recovered or lost, respectively, and stable if no change had occurred. Each patient returned to the clinic for examination and tests. All results were considered at 12 months.

Postoperative transitory or definitive diabetes insipidus was classified in morbidity.

**Ophthalmological Examination**

Before and after surgery, patients underwent a complete ophthalmological examination of visual acuity, visual field, and eye fundus. Visual acuity was considered normal at 20/10. Visual field was tested with an automated perimeter. A mean deviation of 1 dB for the affected eye was considered significant.

In comparing the postoperative and preoperative results, we classified a patient’s condition as normal if all parameters normalized, improved if 1 of the parameters improved, stable if there was no change, and worsened in any other situation. All results were considered at the time of the 12-month follow-up.

**Pathological Diagnosis**

Fragments of all tumors were fixed in Bouin fixative and processed normally for paraffin embedding. Five-micrometer-thick sections were stained with Herlant tetrazochrome and PAS Orange, and immunocytochemistry was performed according to the avidin-biotin-peroxidase method for PRL, GH, ACTH, FSH, LH, TSH, and α-subunit for glycoproteins. The following antibodies were used: monoclonal anti-PRL (1:400, Immunotech), polyclonal anti-GH (1:15000, NIDDK), monoclonal anti-ACTH (1:20000, gift of MP Dubois), monoclonal anti-βFSH (1:6000, Immunotech), monoclonal anti-βLH (1:8000, NIDDK), monoclonal anti-βTSH (1:150, Immunotech), and monoclonal anti-α–subunit (1:150, Immunotech). Tumors were classified via immunocytochemistry according to the WHO classification. They were considered immunonegative when no hormone was detected. Tumors immunopositive for one hormone without clinical or biological signs were classified as silent adenomas.

**Statistical Analysis**

The quality of microscopic and endoscopic removal was compared using a Fisher exact test. Initial characteristics of the 2 groups were compared using a Fisher exact test for qualitative variables or a Student t-test for quantitative variables. Items were considered statistically significant if the probability value was < 0.05. Statistical analyses were computed using the SAS software, version 9.1.3 (SAS, Inc.).

**Results**

**Study Population**

The general characteristics of the 2 groups of patients are summarized in Table 1. Except for histological parameters, with fewer silent and immunonegative adenomas in Group B as compared with Group A, no statistical difference was observed between the 2 groups, particularly with regard to tumor volume, tumor height, and cavernous sinus invasion.

**Quality of Removal**

Whichever technique was used, the goal of surgery was to achieve GTR.

**Considering the Whole Population.** As confirmed on postoperative MR imaging, GTR was achieved in 61 (74%) of 82 patients in Group A compared with 41 (50%) of 82 patients in Group B (p = 0.002; Table 2). Postoperatively, 5 cases of noncompressing suprasellar remnants were noticed in Group A, whereas among the 10 cases of suprasellar remnants in the Group B, 3 were found to compress the optic chiasm and required additional surgery. No intrasellar tumor remnant was found in Group A, compared with 11 cases in Group B.

**According to Tumor Height.** In Group A, the mean tumor height was 25.91 mm (range 10–50 mm; Fig. 1 and Table 1). Gross-total resection was achieved in 94% of cases in which the tumor was < 20 mm, in 76% for lesions between 20 and 30 mm, and in 53% for lesions > 30 mm.

In Group B, the mean height of the tumors was 26.3 mm (range 12–46 mm). Gross-total resection was achieved in 73% of cases in which the tumor height was < 20 mm, in 53% for those between 20 and 30 mm, and in 19% for those > 30 mm. The superiority of endoscopy was significant when considering tumors between 20 and 30 mm (p = 0.02) and tended toward significance for tumors > 30 mm (p = 0.07).

**According to Lateral Extension.** Grade 0 or 1 non-invasive tumors were completely removed in > 90% of cases in both patient groups (Fig. 2). Concerning the Grade 2 and 3 tumors, in most cases considered as invasive, the endoscopic technique was significantly better at controlling and removing the lateral extension, with GTR
achieved in 88% and 67.9% of respective cases versus only 47.8% \( (p = 0.02) \) and 16.7% \( (p < 0.001) \) using the microscopic technique. Lastly, none of the Grade 4 tumors were completely removed.

**Ophthalmic Postoperative Status**

There was no significant difference in postoperative ophthalmic status between the 2 patient groups (Table 3). Among the entire series, none of the patients with normal preoperative examination results worsened. One hundred percent of the patients treated using the endoscopic technique improved (allowing a normal personal and professional life) or normalized compared with 93% in Group B \( (p = 0.35) \). Three patients in Group B did not recover and 1 worsened due to a postoperative suprasellar tumor remnant with hematoma requiring a second intracranial surgical intervention.

**Endocrinological Postoperative Outcome**

When anterior pituitary function was normal before surgery, 29% of patients in Group B compared with only 13.5% of those in Group A worsened postoperatively, although this difference was not significant \( (p = 0.14) \; (Table 4) \).

Pituitary deficiency is a frequent feature associated with NFPAs. For patients suffering a partial pituitary deficit, endoscopy allowed a total or partial recovery in 56% of patients in Group A compared with only 25% in Group B \( (p = 0.01) \). The entire pituitary axis was capable of recovery without any difference between the 2 techniques. Very few patients normalized or improved in the group presenting with a total anterior pituitary deficit.

**Postoperative Complications**

There were no postoperative deaths in this series. Complications are summarized in Table 5. In the entire series, the main difference between the 2 groups concerned CSF leaks (including intra- and postoperative, spontaneous and provoked, minor and major). Cerebrospinal fluid leakage occurred in 7 patients \( (8.5\%) \) from Group B, all of whom were treated with lumbar drainage, and in 10 patients \( (12.1\%) \) from Group A, 9 of whom were successfully treated with lumbar drainage for 5–8 days and the other with a second surgery for reconstruction of the sellar defect. During surgery, a persistent fistula was detected at the superior part of the sellar due to inferior

---

**TABLE 1: Summary of characteristics in 164 patients with NFPAs**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Endoscopic Op</th>
<th>Microscopic Op</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>total no. of patients</td>
<td>82</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>age in yrs</td>
<td></td>
<td>0.94†</td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>57.00</td>
<td>56.50</td>
<td></td>
</tr>
<tr>
<td>range</td>
<td>20–82</td>
<td>27–84</td>
<td></td>
</tr>
<tr>
<td>M/F ratio</td>
<td>47:35</td>
<td>51:31</td>
<td>0.52</td>
</tr>
</tbody>
</table>

**TABLE 2: Tumor removal in the entire study population**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Endoscopic Op</th>
<th>Microscopic Op</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTR (%)</td>
<td>61 (74)</td>
<td>41 (50)</td>
<td>0.002</td>
</tr>
<tr>
<td>STR (%)</td>
<td>21 (26)</td>
<td>41 (50)</td>
<td></td>
</tr>
<tr>
<td>tumor remnant location</td>
<td></td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>cavernous sinus</td>
<td>16</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>suprasellar (compressive)</td>
<td>5 (0)</td>
<td>10 (3)</td>
<td></td>
</tr>
<tr>
<td>intrasellar</td>
<td>0</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

* STR = subtotal resection.
Endoscopy improves the surgical outcome of NFPA migration of the graft positioned during the first surgery. Additional fat graft and fibrin glue were used, and an intrasphenoidal balloon was inserted for 3 days to avoid such a migration.

**Discussion**

Though only recently introduced to pituitary surgery, endoscopy is fast becoming the technique of choice at more and more neurosurgical centers. Combined with the endonasal approach, this technique undoubtedly allows a relatively painless postoperative course for patients. However, its superiority is still under debate in the absence of randomized studies and few series published to date. Nonfunctioning pituitary adenomas together comprise the gonadotrophic (FSH, LH, α–subunit immunostaining), immunonegative (no immunostaining), and silent adenomas (PRL, TSH, ACTH, and GH immunostaining without clinical symptoms). While these adenomas are different in terms of their growth behavior, all represent the same challenge for the neurosurgeon. Indeed, such macroadenomas, for which there is no efficient medical therapy, must be removed via radical surgery whenever possible. Considering the literature reports of postoperative residue in 35.5%–74% of cases treated using a microscopic technique and our own experience of only a 50% rate of GTR, there is clearly room for refinement. Our main goal was to investigate whether endoscopy does indeed contribute toward the improved removal of NFPA.
As mentioned above, NFPAs are difficult to remove because of their suprasellar and lateral extension.\(^9\) In our experience, the use of \(^0\) and angled endoscopes able to explore the entire surgical field improves tumor control and allows 74\% total removal, which is comparable with rates in the “endoscopic” literature (56\%–93\%),\(^3,4,11,15,22,29,30\) as opposed to 50\% total removal via microsurgery, which is comparable with rates in the “microscopic” literature (35\%–74\%); Table 6).\(^13,14,30,33,37,40\) Whatever the height of the adenoma, endoscopy improved control of the suprasellar part, with only 5 noncompressive residues in Group A versus 10 residues in Group B, of which needed reoperation due to persistent compressive effect. Endoscopy also helped us gain control over lateral extension of the tumor. The medial wall of the cavernous sinus cannot be seen on the 1.5-T MR imaging used in this study. Indirect arguments are therefore required to quantify this important point. The Knosp classification\(^31\) was used as a simple and easy method of quantifying cavernous sinus invasion. Based on a tumor’s relation to the carotid lines, Knosp et al.\(^31\) defined 4 grades. Grade 0–1 lesions are clearly noninvasive and accessible for complete removal. In that subgroup of tumors, in which adenomas are mostly suprasellar, both techniques produced similar results with 90\% GTR. When the tumor undoubtedly invaded the cavernous sinus (Grade 4), as expected, whichever technique was used, the tumor removal was always subtotal. More interesting are the Grade 2 and 3 groups, within which the tumor crosses the cross-sectional centers of the intra- and supracavernous ICA. In Knosp and colleagues’ original study, these tumors were considered as invading the cavernous sinus. Our results obtained with endoscopy (88\% and 67.9\% GTR for Grade 2 and 3 tumors, respectively), when compared with those achieved with microsurgery (47.8\% and 16.7\%, respectively), clearly demonstrated the improvement in terms of the visual field offered by the endoscope, which enabled increased lateral exploration and thus a more efficient and safe removal of the adenoma. Our results do, however, raise an important debate regarding actual invasion of the cavernous sinus by such adenomas. Grade 2 lesions, with the same rate of GTR as the Grade 0–1 lesions, are probably noninvasive and just pushing away the medial wall of the cavernous sinus, although a microscopic invasion cannot be excluded. Actual invasion seems to occur at the Grade 3 level, at which one-third of the tumors in our endoscopic group were subtotally removed. We were unable to correlate the Knosp grading with the perioperative aspect of the medial wall of the cavernous sinus as some data were missing. However, a prospective study of this topic is ongoing.

Nevertheless, we are aware that this study has some weaknesses. First, it is a retrospective and not a randomized study, difficult to design in practice. Second, the neuronavigation system was used only for the patients in Group A, primarily to guide the endonasal step. In our opinion, this had a minor if any impact on the tumor resection and thus a more efficient and safe removal of the adenoma. However, the included microscopic cases were the latest after more than 1300 cases treated previously at our center. On the other hand, all patients in the endoscopic group were taken into account, including those treated at the beginning of our endoscopic experience, which might have negatively affected the results of Group A. Finally, our findings support those of others arguing in favor of a beneficial impact of endoscopy on pituitary surgery, with higher rates of GTR in the endoscopic series compared with the microscopic one (Table 6). However, while endoscopy does appear to improve immediate surgical outcome with fewer postoperative residues on MR

### TABLE 3: Postoperative ophthalmological status

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal vision (%)</td>
<td>stable</td>
<td>25/25 (100)</td>
<td>20/20 (100)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Visual impairment (%)</td>
<td>worsened</td>
<td>0</td>
<td>1/62 (2)</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td></td>
<td>stable</td>
<td>0</td>
<td>3/62 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>improved</td>
<td>29/57 (51)</td>
<td>31/62 (50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>normalized</td>
<td>28/57 (49)</td>
<td>27/62 (43)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 4: Postoperative endocrinological outcome

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (%)</td>
<td>unchanged</td>
<td>37</td>
<td>31</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>worsened</td>
<td>32 (86.5)</td>
<td>22 (71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 (13.5)</td>
<td>9 (29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAPI (%)</td>
<td>worsened</td>
<td>32</td>
<td>41</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>unchanged</td>
<td>7 (22)</td>
<td>12 (29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>improved</td>
<td>7 (22)</td>
<td>19 (46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>normalized</td>
<td>2 (6)</td>
<td>4 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAPD (%)</td>
<td>unchanged</td>
<td>13</td>
<td>10</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>improved</td>
<td>10 (76.9)</td>
<td>6 (60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>normalized</td>
<td>1 (7.7)</td>
<td>2 (15.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* PAPI = partial anterior pituitary insufficiency; TAPD = total anterior pituitary deficiency.

### TABLE 5: Postoperative complications*

<table>
<thead>
<tr>
<th>Complication</th>
<th>Endoscopic Op</th>
<th>Microscopic Op</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>4 (4.9)</td>
<td>1 (1.2)</td>
<td>0.37</td>
</tr>
<tr>
<td>CSF leakage</td>
<td>10 (12.1)</td>
<td>7 (8.5)</td>
<td>0.33</td>
</tr>
<tr>
<td>Meningitis</td>
<td>3 (3.7)</td>
<td>4 (4.9)</td>
<td>1</td>
</tr>
<tr>
<td>Definitive DI</td>
<td>7 (8.5)</td>
<td>8 (9.8)</td>
<td>1</td>
</tr>
<tr>
<td>Hematoma</td>
<td>0</td>
<td>1 (1.2)</td>
<td>1</td>
</tr>
<tr>
<td>CN III transient palsy</td>
<td>0</td>
<td>2 (2.4)</td>
<td>1</td>
</tr>
</tbody>
</table>

* DI = diabetes insipidus.
endoscopy improves the surgical outcome of NFPA

Two other studies of microscopically removed NFPA, one by Nelson et al. (among 83 patients, 35% improved, 32.1% worsened, and 32.1% stabilized), and another by Jane and Laws (among 1000 patients, 27% improved), reported less optimistic results that more closely resemble the own experience (improved or normalized in 25%, unchanged in 46%, and worsened in 29%). Endocrinological data for endoscopy in NFPA surgery are sparse. While no definitive conclusions can yet be drawn from our observations, endoscopy does seem to improve the preservation of pituitary function. Finally, permanent diabetes insipidus is not rare in the postoperative course of such macroadenoma removals, in which the posterior pituitary has in most cases completely disappeared.

With regards to surgical morbidity, CSF leaks seem to be the most common and disturbing complication for pituitary surgeons and their patients. In comparing the 2 techniques at our institution, CSF leaks were observed in 12.1% of patients using the endoscopic technique (p = not significant). It should be noted that most CSF leaks were minor and easily managed with packing and CSF diversion. In the largest endoscopic study in the literature, the percentage of CSF leaks ranged from 1.6% to 5.2%, lower rates than that reported here. In a series of 592 pituitary macroadenomas and giant pituitary adenomas removed via the microscopic technique, Han et al. reported postoperative CSF leaks in 4.4% of patients and described a correlation between the risk of CSF leaks and the size of the adenoma, its consistency, margins, and size. The same prognostic markers were observed in our study (data not shown). The difference between our observations and those of others can be at least partly explained by the heterogeneity of the series, that is, grouping together macro- and microadenomas and secreting or nonsecreting tumors. In addition, only significant CSF leaks are often taken into account in the literature. Ciric et al. published the results of a survey of American neurosurgeons, including the surgical results of 958 neurosurgeons, and reported CSF leaks in 1.5% of cases (mixing all types of adenomas).

imaging, further studies with large multicentric cohorts are warranted to demonstrate the real impact of such a technique on long-term recurrence, which is the main issue with such adenomas.

With regards to the ophthalmological outcome, the 2 techniques were similar. Patients can therefore expect to recover enough vision to resume a normal life except in the rare event of optic nerve atrophy or complications (none in our endoscopic group). This finding is in accordance with reports in the literature. Indeed, Frank et al. reported 94.7% normalization or improvement, 3.8% stabilization, and 1.2% worsening; Tabace et al. reported 92% complete resolution or significant improvement with no experience of worsening; and Dehdashti et al. reported 91% normalization or improvement and 9% stabilization.

More interesting is the endocrinological outcome. In more aggressive tumor removal using the endoscope, one might expect more significant pituitary deficiency. In our experience, however, during surgery in many cases, a thin layer of anterior pituitary tissue can be seen after removing the tumors with the endoscope pushed inside the sella (never seen during microscopic surgery), suggestive of better-preserved pituitary function. Thus, using the endoscopic technique, less aggravation and significantly more improvement has been observed mainly in the group experiencing partial anterior deficits (56% normalized or improved in the endoscopic group compared with 25% in the microscopic surgery group, p = 0.01). In the literature, while numerous studies have been published on the endocrinological outcome of hypersecretion syndromes in patients with pituitary adenomas, only a few have focused on the impact of NFPA surgery on pituitary function. The largest study was published by Nomikos et al., who described the endocrinological outcome of 660 NFPA surgically removed via the microscopic technique with a 12-month follow-up. Patients with partial anterior pituitary insufficiency normalized or improved in 49.7% of cases, remained stable in 48.9%, and worsened in 1.4%.

Endoscopy improves the surgical outcome of NFPA

TABLE 6: Quality of tumor removal in NFPA series following endoscopy and microsurgery

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of NFPA Cases</th>
<th>No. of CSI Cases (%)</th>
<th>% GTR of All Endoscopy</th>
<th>% GTR of All Microsurgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ebersold et al., 1986</td>
<td>100</td>
<td>unknown</td>
<td>NA</td>
<td>50.0</td>
</tr>
<tr>
<td>Saito et al., 1995</td>
<td>100</td>
<td>unknown</td>
<td>NA</td>
<td>74.0</td>
</tr>
<tr>
<td>Zhang et al., 1999</td>
<td>208</td>
<td>unknown</td>
<td>NA</td>
<td>70.2</td>
</tr>
<tr>
<td>Jho et al., 2001</td>
<td>68</td>
<td>unknown</td>
<td>78</td>
<td>NA</td>
</tr>
<tr>
<td>Cappabianca et al., 2002</td>
<td>80</td>
<td>19 (24)</td>
<td>56</td>
<td>NA</td>
</tr>
<tr>
<td>Kabil et al., 2005</td>
<td>161</td>
<td>unknown</td>
<td>93</td>
<td>NA</td>
</tr>
<tr>
<td>Mortini et al., 2005</td>
<td>378</td>
<td>unknown</td>
<td>NA</td>
<td>64.8</td>
</tr>
<tr>
<td>Ferrante et al., 2006</td>
<td>295</td>
<td>unknown</td>
<td>NA</td>
<td>35.5</td>
</tr>
<tr>
<td>Frank et al., 2006</td>
<td>173</td>
<td>35 (20)</td>
<td>76.9</td>
<td>NA</td>
</tr>
<tr>
<td>Dehdashti et al., 2008</td>
<td>111</td>
<td>10 (9)</td>
<td>88</td>
<td>NA</td>
</tr>
<tr>
<td>present study</td>
<td>164</td>
<td>16 (19.5); 20 (24.5)</td>
<td>74</td>
<td>50.0</td>
</tr>
</tbody>
</table>

* CSI = cavernous sinus invasion; NA = not applicable, technique not used.
† Endoscopy group.
‡ Microscopy group.
These results clearly demonstrate that the percentage risk of CSF leakage, as with other side effects of surgery, can be dramatically decreased with experience. However, this learning curve is unavoidable whatever the surgical technique. Experience can be gained fairly rapidly given that in the present study the 22% incidence of CSF leaks in the first 41 operations with the endoscope was reduced to 7.3% for the last 41 operations and is still decreasing, currently at 5% in macroadenomas after more than 400 procedures to date. Meningitis, a potentially fatal complication, can be caused by a CSF leak or can occur after lumbar drainage, although it can usually be easily treated with antibiotics. Seven patients in the present series (4% of patients on average) presented with symptoms of and CSF analyses compatible with meningitis, with no difference between the techniques. According to the literature, for either endoscopy or microscopic surgery, the risk is around 1%. About half of our meningitis cases were caused by contamination by a lumbar drain probably kept in place too long. We have now changed our protocol and perform lumbar drainage over a shorter period of time and only for severe CSF leakage. Pursuing this course has contributed to a decreased incidence of meningitis in our more recent cases to within the range observed in the literature.

A special note should be made of the epistaxis that can occur with an endonasal route (about 1% in the literature and 5% in our endoscopic group). Great care should be taken to avoid the posterior nasal and sphenopalatine arteries situated below the ostium and behind the posterior part of the middle turbinate, respectively. Indeed, the epistaxis encountered in our study arose following injury to these arteries when the lateral recess of the sphenoid was systematically opened and the mucosa was cut from the ostium down to the choana with minimal cauterization. Cauterization of these arteries when a large opening of the sphenoid sinus is required completely resolves this issue.

Conclusions

In this large series of patients with NFPAs, endoscopy has proven to be more efficient than microscopic surgery in terms of the quality of resection and the endocrinological outcome. We therefore recommend that endoscopy be considered as the choice technique for removing such pituitary tumors. Further studies with long-term follow-up are ongoing to establish whether these encouraging results for the short term have a positive impact on long-term tumor recurrence for the different subtypes of NFPAs, a critical issue with such adenomas.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Jouanneau. Acquisition of data: Jouanneau, Messerer, De battista, Kassis, Dubourg. Analysis and interpretation of data: Jouanneau, Messerer, Lapras, Dubourg, Perrin. Drafting the article: Jouanneau, Messerer, Dubourg. Critically revising the article: Jouanneau, Messerer, Raverot, Trouillas. Reviewed final version of the manuscript and approved it for submission: Jouanneau, Messerer, Raverot, Trouillas, Perrin.

Statistical analysis: Dubourg. Study supervision: Jouanneau.

Acknowledgment

The authors acknowledge Emily Witty for English language editing.

References


M. Messerer et al.
Endoscopy improves the surgical outcome of NFPA


Address correspondence to: Emmanuel Jouanneau, M.D., Ph.D., INSERM U1028, CNRS UMR5292, Centre de Recherche en Neurosciences de Lyon, Equipe Neuro-oncologie et Neuro-inflammation, Faculté de Médecine Lyon Sud, Université de Lyon I, Département de Neurochirurgie A, Hôpital Neurologique Pierre Wertheimer, Groupement Hospitalier Est, Hospices Civils de Lyon, 59 Boulevard Pinel, Bron, F-69500, France. email: emmanuel.jouanneau@chu-lyon.fr.