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Endoscopic Endonasal Transsphenoidal Approach: An Additional Reason in Support of Surgery in the Management of Pituitary Lesions

ABSTRACT—The outcome of endoscopic endonasal transsphenoidal surgery in 10 patients with pituitary adenomas was compared with that of traditional transnasal transsphenoidal approach (TTA) in 20 subjects. Among the 10 individuals subjected to "pure endoscopy," 2 had a microadenoma, 1 an intrasellar macroadenoma, 4 had a macroadenoma with suprasellar expansion, 2 had a macroadenoma with supra-parasellar expansion, and 1 a residual tumor; 5 had acromegaly and 5 had a nonfunctioning adenoma (NFA). Among the patients subjected to TTA, 4 had a microadenoma, 2 had an intrasellar macroadenoma, 6 had a macroadenoma with suprasellar expansion, 4 had a macroadenoma with supra-parasellar expansion, and 4 had a residual tumor; 9 patients had acromegaly, 1 hyperprolactinemia, 1 Cushing's disease, and 9 a NFA. At the macroscopic evaluation, tumor removal was total (100%) after endoscopy in 9 patients and after TTA in 14 patients. Six months after surgery, magnetic resonance imaging (MRI) confirmed the total tumor removal in 21 of 23 patients (91.3%). Circulating growth hormone (GH) and insulin-like growth factor-I (IGF-I) significantly decreased 6 months after surgery in all 14 acromegalic patients: normalization of plasma IGF-I levels was obtained in 4 of 5 patients after the endoscopic procedure and in 4 of 9 patients after TTA. Before surgery, pituitary hormone deficiency was present in 14 out of 30 patients: pituitary function improved in 4 patients, remaining unchanged in the other 10 patients. Visual field defects were present before surgery in 4 patients, and improved in all. Early surgical results in the group of 10 patients who underwent endoscopic pituitary tumor removal were at least equivalent to those of standard TTA, with excellent postoperative course. Postsurgical hospital stay was significantly shorter (3.1 ± 0.4 vs. 6.2 ± 0.3 days, $p < 0.001$) after endoscopy as compared to TTA.

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Transsphenoidal surgery is a milestone in the treatment of secreting[1–13] and clinically nonfunctioning pituitary adenomas (NFA)[2,14–16] as well as of other tumors occurring in the pituitary fossa.[17–22] A technical refinement in pituitary surgery allows a progress itself and can allow other specialists involved in the treatment of pituitary diseases to enlarge their possibilities of approach, with better final result for individual patients. In keeping with this perspective, Jho et al.[23] have been recently proposed the adoption of a one-nostril endoscopic endonasal transsphenoidal procedure, characterized by an improved respect for the nose and the sphenoidal sinus and by a wider possibility of management of the pituitary fossa.

To evaluate if this simple and effective, minimally traumatic approach permits further development in the overall management of pituitary tumors, we compared the outcome of endoscopic endonasal transsphenoidal surgery in 10 patients treated during 1997, with that of traditional transnasal transsphenoidal approach (TTA) performed in the last consecutive 20 patients admitted to our Institution in 1996. The efficacy of surgery was assessed by macroscopic evaluation during surgery, postsurgical magnetic resonance imaging (MRI), and hormone profile in secreting adenomas.

MATERIALS AND METHODS

Patients

From January to June 1997, 10 patients (6 males, 4 females, age range 33 to 67 years) with pituitary adenomas were subjected to endoscopic endonasal surgery. Five had acromegaly, while the remaining 5 had a NFA. Among these 10 patients, 2 had a microadenoma (nos. 3 and 4, Table 1), 1 had an intrasellar macroadenoma (no. 7, Table 1), 4 had a macroadenoma with suprasellar expansion (nos. 2, 5, 9, and 10, Table 1), 2 had a macroadenoma with supra and parasellar expansion (nos. 1 and 8, Table 1), and the remaining patient had a residual tumor mass (no. 6, Table 1). Twenty patients (11 males, 9 females, age range 20 to 68 years) consecutively operated on for pituitary adenoma via TTA served as a control. Six patients had a GH-secreting adenoma, 1 a prolactin (PRL)-secreting adenoma, 3 a growth hormone (GH)-PRL-secreting adenoma, 1 had a corticotropin (ACTH)-secreting adenoma and, 9 had an NFA. Among these 20 patients, 4 had a microadenoma (nos. 11, 19, 24, and 25, Table 1), 2 had an intrasellar macroadenoma (nos. 14 and 20, Table 1), 6 had a macroadenoma with suprasellar expansion (nos. 16, 18, 21, 26, 28, and 30, Table 1), 4 had a macroadenoma with supra and parasellar expansion (nos. 12, 13, 15, and 17, Table 1) and the remaining 4 had a residual tumor mass (nos. 22, 23, 27, and 29). Acromegaly was diagnosed on the basis of clinical features, elevated GH serum levels not suppressible below 1 ng/mL by oral glucose administration, elevated plasma insulin-like growth factor-1 (IGF-1) plasma levels for age.[24] To improve cardiovascular, respiratory and metabolic conditions, all acromegalic patients underwent a short period of medical treatment with octreotide, a long-lasting somatostatin analogue, before surgery.[25] The diagnosis of hyperprolactinemia was established on the basis of physical examination and the evidence of high PRL levels assayed during a diurnal profile with 30-min samples (8.00–14.00). Cushing's disease was diagnosed in keeping with lack of circulating ACTH and cortisol circadian rhythm, increased urinary free cortisol levels, lack of cortisol suppression after low-dose and greater than 50% suppression after high-dose dexamethazone test. NFA was diagnosed in absence of clinical features of hormone hypersecretion as well as of increase in circulating pituitary hormones. Patients' profile at study entry is shown in Table 1.

Surgical Technique

An endoscopic endonasal procedure, according to a slightly modified Jho-Carrau technique[23,26,27] for the transsphenoidal removal of pituitary lesions, was carried out via one nostril in 10 cases.[28] No speculum was used. All the instruments are inserted through the same nostril, close and parallel to the endoscope. After the middle turbinate is pushed laterally, the sphenoidal ostium is enlarged. The sphenoidal mucosa is partially removed, just to allow a better anatomical orientation: the 0° endoscope (or, even better, the 30° endoscope) gives a panoramic view of the sphenoidal sinus content, with the anterior wall of the sella and the optic and carotid protuberances. The sellar time takes place just as in common transsphenoidal operations, but with the advantage of a direct visualization into the anatomy of all the structures: the interface adenoma-gland can be easily distinguished, so as the suprasellar cistern and the medial wall of the cavernous sinuses, with a possibility of a more accurate and safe tumor removal. No nasal packing is used at the end of the procedure.

In the other 20 patients a traditional transnasal transsphenoidal procedure was performed.

Complete removal was considered when 100% of the adenomatous tissue was removed at surgery. The removal of 80–90% of the lesion was considered subtotal and less than 80% was considered partial removal.

Magnetic Resonance Imaging

MRI (0.5 Tesla, Vectra, GE) was carried out with T1-weighted spin echo (SE) sequences, 3-mm slides, in coronal and sagittal sections, before and after contrast

Table 1. Patients Profile at Study Entry

				Presurgical Evaluation				Postsurgical Evaluation		
								Tumor removal		
Patient (sex, age)	Final Diagnosis	Previous Treatment	MRI study	Serum GH (ng/mL)	Serum PRL (ng/mL)	Plasma ACTH pg/mL)	Pituitary hormone deficiency	macroscopic evaluation	MRI	hospital stay (days)
Functional endoscopic pituitary surgery										
1.f,33	NFA	brc	I,S,rP MA	1.1	77.5	18.6	FSH,LH	total	total	2
2.m,36	GH MA	oct	I,S MA	410	6.7	46	none	total	total	6
3.m,45	GH ma	oct	l-sided ma	55	6.3	28.8	none	total	total	4
4m,45	GH ma	oct	r-sided ma	85	17.5	45	none	total	total	3
5.f,52	NFA	none	I,S MA	0.5	22.4	4.0	FSH,LH	total	total	2
6.m,54	NFA	TS surgery	I,S MA	2.2	17.6	16.0	ACTH	total	total	2
7.f,59	GH MA	oct	IMA	30	8.2	30	none	total	total	4
8.m,62	NFA	none	I,S,rP MA	0.2	17.2	16	none	subtotal	subtotal	2
9.m,65	NFA	none	I,S MA	0.2	5.4	22.0	hypopituitarism	total	total	4
10.f,67	GH MA	oct	I,S MA	33.5	63.6	18.8	none	total	total	2
Classic transnasal transsphenoidal surgery										
11.f,19	GH ma	none	r-sided ma	75.3	18	59	none	total	total	4
12.f,20	GH-PRL MA	oct	I,S, lP MA	23.8	44.9	80	none	partial	partial	7
13.f,22	GH-PRL MA	oct,brc	I,S,rP MA	190	85	73	none	partial	partial	5
14.f,26	NFA	cab	IMA	2.5	127	91	none	total	partial	6
15.m,29	GH-PRL MA	oct,brc	I,S,l, and rP MA	65.6	500	104	FSH,LH	partial	partial	7
16.m,29	GH MA	oct	I,S MA	120	1.2	26.0	none	total	total	5
17.m,29	PRL MA	none	I,S,l, and rP MA	1.8	5850	30.0	FSH,LH,ACTH	partial	partial	6
18.f,31	NFA	none	I,S MA	0.1	44.8	25.6	FSH,LH	total	total	7
19.m,31	GH ma	oct	l-sided ma	32.6	6	42	none	total	total	5
20.f,32	NFA	none	IMA	2.5	91.6	48	none	total	total	7
21.m,33	NFA	none	I,S MA	1.6	12	24.8	FSH,LH	total	total	4
22.f,37	NFA	TS surgery	I,S,lP MA	17.6	19	74.6	hypopituitarism	partial	partial	7
23.f,38	NFA	TS surgery	I,S MA	0.1	55.7	52.0	FSH,LH	total	total	10
24.m,43	GH ma	oct	l-sided ma	25	9.4	88	none	total	total	5
25.m,47	ACTH ma	none	r-sided ma	0.1	10.0	169.0	none	total	total	6
26.m,48	NFA	none	I,S MA	0.3	13.0	104.0	FSH,LH	total	total	5
27.m,53	GH MA	TS surgery,oct	I,S,rP MA	36	13.0	95.0	ACTH,TSH	partial	partial	9
28.m,57	GH MA	oct	I,S MA	155	35	55.3	none	total	partial	7
29.f,58	NFA	TS surgery	I,S MA	0.4	34	98.3	FSH,LH,TSH	total	total	6
30.m,68	NFA	none	I,S MA	2.1	15.9	41.8	hypopituitarism	total	total	6

MA = macroadenoma; ma = microadenoma; NFA = nonfunctioning adenoma; TS = transsphenoidal; oct = octreotide; brc = bromocriptine; cab = cabergoline; I = intrasellar; S = suprasellar; r = right; l = left; and P = parasellar. Normal ranges: GH, 0–5 ng/mL; PRL, 5–25 and 5–15 ng/mL in females and males, respectively; ACTH at 8.00 a.m., 10–130 pg/mL. Tumor removal was graded as follows: 100% as total, 80–90% as subtotal, <80% as partial.

enhancement with Gadolinium-diethylenetriamine pentaacetic acid (DTPA). Sellar MRI was carried out before and 6 months after surgery to evaluate tumor removal. The total, subtotal, or partial removal of the pituitary lesion was considered as reported from the macroscopic evaluation at surgery.

Endocrinological Evaluation

A complete endocrinological profile, including basal and stimulated hormone release, circulating GH and PRL assay in multiple sampling, thyrotropin (TSH) and total and free thyroid hormones, ACTH, cortisol (at 8.00 am and 6.00 pm) and urinary free cortisol, was performed in all patients, before and 6 months after surgery.

Assays

Serum GH levels were assayed by radioimmunoassay (RIA) using kits provided by Radim (Pomezia, Italy): in line with the literature,[29] cure of GH-secreting adenomas was considered when basal GH levels were below 2.5 ng/mL and plasma IGF-I levels were normalized for age. Plasma IGF-I levels were assayed by immunoradiometric assay (IRMA) using kits provided by Diagnostic System Laboratories, Inc. (DSL), (Webster, TX): in our laboratory the normal IGF-I range in 20–40 years and in 40–60 years aged adults was 110–385 and 65–320 ng/mL, respectively. Circulating PRL, follicle-stimulating hormone (FSH), and LH levels were assessed by RIA using available commercial kits. The normal ranges were: PRL, 5–15 in males and 5–25 ng/mL, in females; FSH and LH, 5–18 IU/mL. Circulating ACTH and cortisol levels were assayed by IRMA and RIA, respectively, using SORIN kits (Saluggia, Italy); the normal ranges were: 10–130 pg/mL and 50–250 ng/mL at 8 a.m., respectively.

Statistical Analysis

The statistical analysis was performed by the two-tailed Student's *t*-test for paired data and by analysis of variance (ANOVA) where appropriate. Data are shown as Mean ± SEM. Significance was set at 5%.

RESULTS

At the macroscopic evaluation, tumor removal was total in 9 of 10 patients operated by endoscopy (see Fig. 1) and in 14 out of 20 operated by TTA. Tumor removal was subtotal in 1 patient of the first group (no. 8, Table 1) with a huge intra-, supra-, and right parasellar NFA.

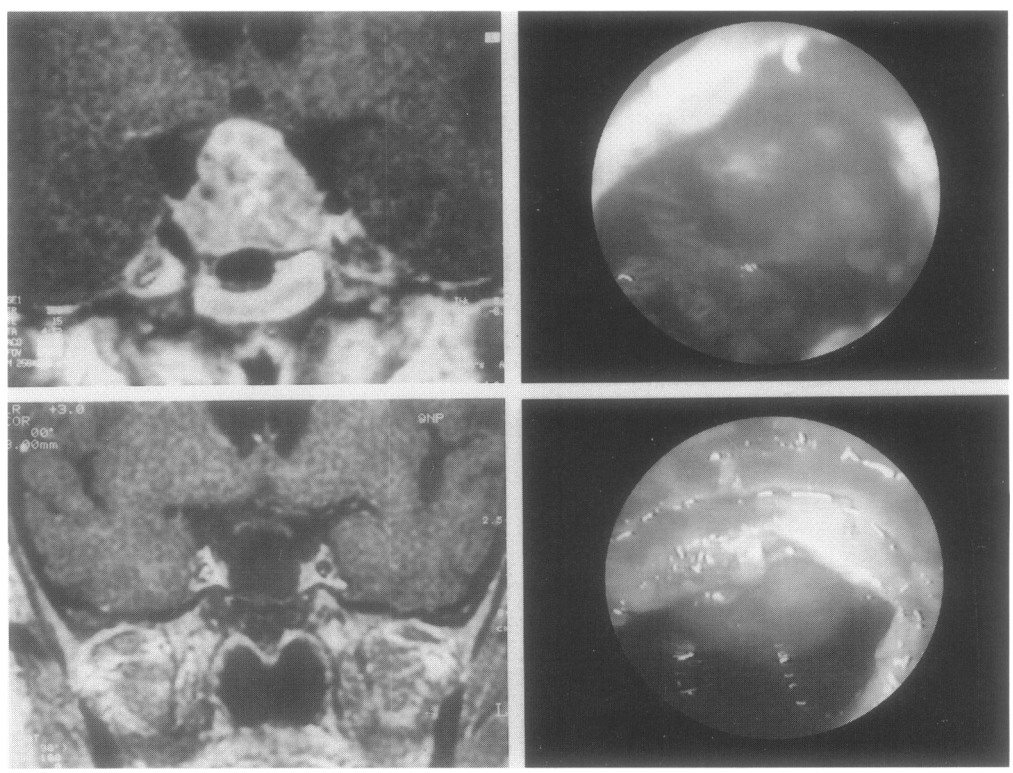

Figure 1. Coronal study at Magnetic Resonance Imaging (MRI) of a large residual nonfunctioning pituitary adenoma before functional endoscopic pituitary surgery (top, left), macroscopic appearance at operation (top, right), MRI study carried out 6 months after operation (bottom, left), sellar cavity immediately after adenoma removal (bottom, right).

After, TTA tumor removal was partial in 1 PRL-secreting macroadenoma (no. 17, Table 1), in 3 GH-PRL-secreting tumors (nos. 12, 13, 15, Table 1) and in two residual tumors (1 NFA and 1 GH-secreting adenoma, with involvement of the cavernous sinuses (nos. 22 and 27, Table 1).

Six months after operation, MRI confirmed the complete tumor removal in 21 out of 23 patients (91.3%): in these 2 patients operated on by TTA (nos. 14 and 28, Table 1), MRI documented the presence of a small tumor remnant, not visualized macroscopically during surgery. In the only patient with subtotal removal after the endoscopic approach, MRI revealed the persistence of a small intrasellar tumor remnant (see Fig. 2), likely due to the inadequate exposure of the sellar floor.

As far as endocrine function was concerned, circulating GH and IGF-I significantly decreased 6 months after surgery in all 14 patients with acromegaly (see Fig. 3). Suppression of serum GH levels below 2.5 ng/mL was achieved in 4 of 5 patients operated through endoscopy and in 4 out of 9 patients operated on via TTA. Normalization of plasma IGF-I levels was obtained in 4 patients after endoscopy and in 3 patients after TTA (Fig. 3). After surgery, hyperprolactinemia disappeared in 2 patients with acromegaly (nos. 10 and 12, Table 1) and in 4 patients with NFA (nos. 1, 18, 20, and 23, Table 1). Before surgery, pituitary hormone deficiency was present in 14 out of 30 patients (see Table 1). Six months after surgery, hypogonadism resolved in 4 patients (nos. 1, 18, 20, and 26). Pituitary function remained unchanged in the other 10 patients. Replacement therapy was not modified by surgery in any patient. Visual field defects were present before surgery in 4 patients (nos. 8, 17, 20 and 25, Table 1) and improved in all. Transient diabetes insipidus (water balance greater than 4 L/day) was recorded in 4 patients after the endoscope procedure (nos. 3, 4, 6, and 9) and in 2 patients after TTA (nos. 12 and 21).

Postsurgical hospital stay was significantly shorter (3.1 ± 0.4 vs. 6.2 ± 0.3 days, $p < 0.001$) after endoscopy as compared to TTA (see Table 1).

DISCUSSION

Transsphenoidal neurosurgery for the treatment of pituitary tumors started ideally a century ago, in 1897, thanks to the studies of Giordano,[30] an Italian Anatomist. He showed the possibility to overcome the more invasive transcranial route, so that the sellar floor was then reached via a transfacial approach and, a few years later, through transnasal or transoral ways. Standard microsurgical transsphenoidal operations demonstrated relevant advantages in comparison to the transcranial approach because they do not require a craniotomy, with reduced trauma and operative risk. They offer a decreased postoperative hospital stay and are better accepted by patients. The main limitation of the transsphenoidal approaches is the necessity to adopt a nasal speculum that determines a restriction of the intraoperative visual field. Moreover, otolaryngological and orodental complications, such as nasal septum perforations

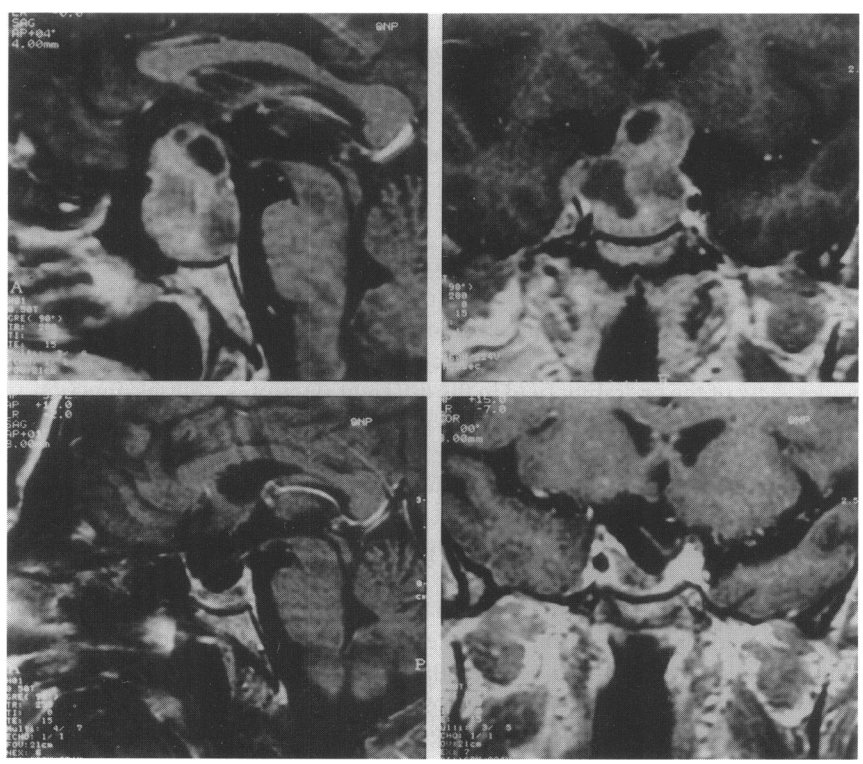

Figure 2. Sagittal and coronal study at Magnetic Resonance Imaging of a nonfunctioning pituitary adenoma (patient no. 8, Table 1) before (top, left and right) and 6 months after functional endoscopic pituitary surgery (bottom, left and right).

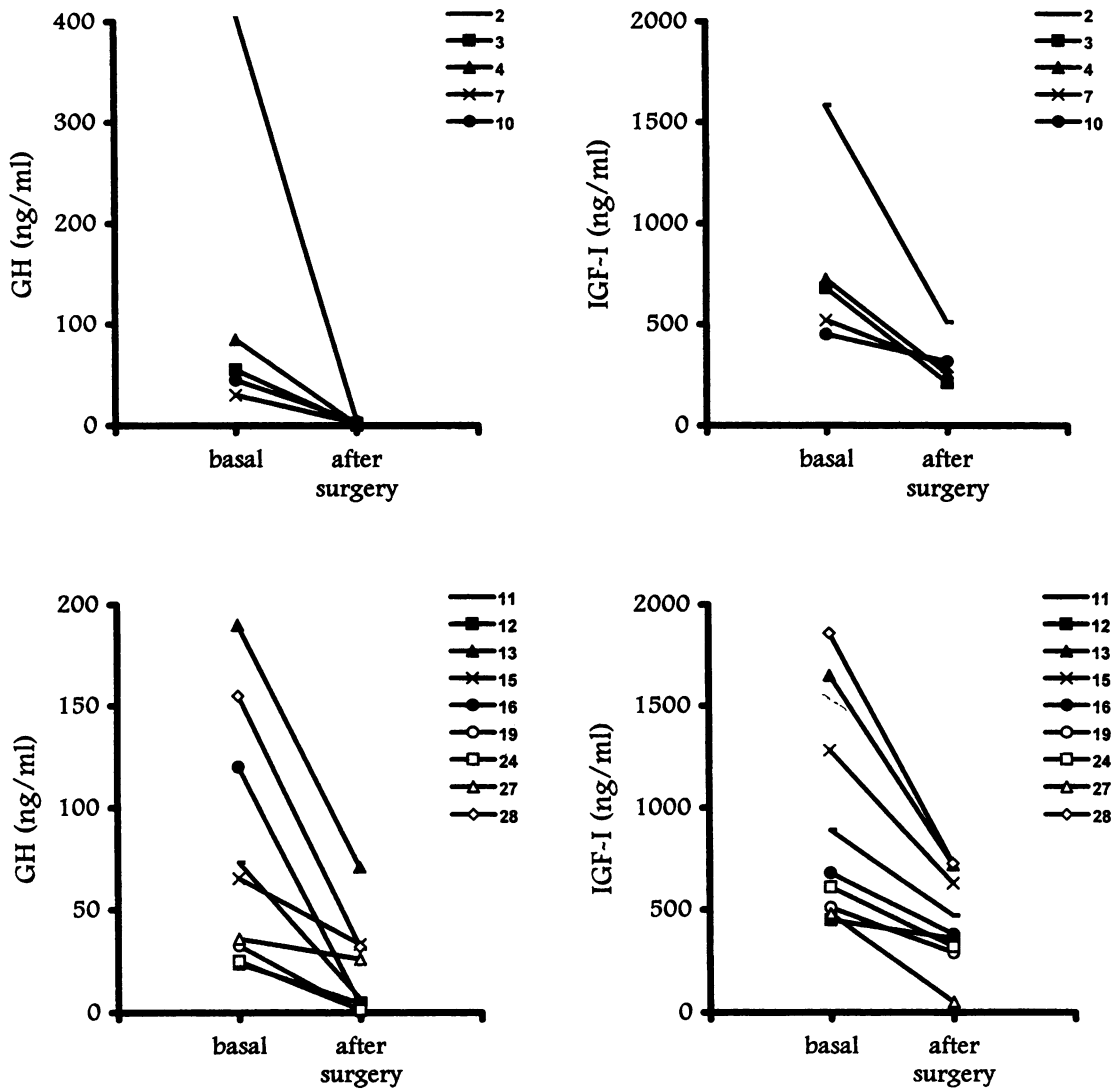

Figure 3. Serum growth hormone (GH) levels (left) and plasma insulin-like growth factor-I (IGF-I) levels (right) before and 6 months after surgery in the five patients with acromegaly treated by functional endoscopic pituitary surgery (top) and in the nine patients with acromegaly treated by traditional transsphenoidal surgery (bottom).

or sinusitis, may occur.[31,32] The way pionereed by Jho et al[23,26,27] is a real innovation because of its simplicity. The endonasal one nostril approach allows the complete respect of the nasal mucosa. This technique allows a wider view of the operating field in the different steps of the operation, as far as it concerns the sphenoidal sinus and the "space" in and over the sella. The anatomical orientation is hence more complete, the movements of the surgeon's hands are not constricted by the speculum and, consequently, the potential for tumor removal is greater. The minimal invasiveness, the effort to guarantee the free air circulation in the paranasal sinuses after the transsphenoidal approach, and the excellent outlook into the sella have opened a new standpoint in the pituitary surgery. Because functional endoscopic sinus surgery (FESS) is the modern otolaryngological surgery for nasal and paranasal diseases, allowing the preservation of the first airways,[33] we proposed the term functional endoscopic pituitary surgery (FEPS) to underline the respect for the regular air circulation and paranasal sinuses function, and the possibility of enhancing the surgical precision in tumor removal with the preservation of the normal pituitary tissue and function.[28]

In this preliminary study, we obtained the total removal of the pituitary lesion in the great majority of the patients operated on by FEPS. This result was achieved also in one patient operated for a large residual NFA. By contrast, in a similar series of patients (treated by the same surgical team) operated on by the classic transsphenoidal approach, we obtained the total removal of pituitary tumors, as confirmed by MRI, in 12 out of 20 patients (60%). In addition, after FEPS normalization of

IGF-I levels was achieved in 4 out of 5 patients. After TTA only 3 out of 9 patients obtained similar results. As far as it concerns the preservation of the normal pituitary function, no impairment of pituitary secretion was recorded after FEPS or TTA and 4 hypo-gonadic patients regained a normal function (1 after FEPS and 3 after TTA).

According to the item of Molitch et al,[34] who states that: "Once the diagnosis of a pituitary tumor has been made it is important to tailor the therapy to the clinical problem and to the needs of the patients," FEPS might be considered a tailored surgery in a contest of tailored therapy. The ease of such new procedure, which bears only minor complications, makes surgical option more versatile, able to consent a radical removal even in cases of large adenomas. There are some peculiar conditions in which FEPS might play an ameliorative role:

1. *Treatment of recurrences* appears much easier with this approach because the already enlarged sphenoidal ostium during the previous TTA makes the sella very quick to reach and to manage, thanks to the wider anatomical orientation.

   On the basis of a careful postsurgical follow-up by serial MRI, we have already suggested, in presence of tumor regrowth NFA, to repeat transsphenoidal surgery[35] as an alternative to radiotherapy, promptly administered if necessary, considering tumor size and invasiveness. Otherwise, the recent introduction of somatostatin analogues or even more of long-acting somatostatin analogs in the treatment of acromegaly has decreased the need for radiotherapy in patients not cured by surgery.[36] Reoperation could be considered together with somatostatin analog treatment to maximize the chance of a cure. For the treatment of recurrences, incompletely excised functioning or NFA not cured by the first surgery and/or medical treatment, FEPS could be used instead or before radiotherapy because of its minimal invasiveness, its wider anatomical control of the presellar phase of the operation, in the sphenoidal sinus (which is particularly helpful facing recurrences) and of its potential of greater and safer tumor removal under direct visual control. FEPS could offer in these patients the possibility of avoiding all the delayed side effects of radiotherapy,[37–40] among which the secondary hypopituitarysm is almost unavoidable.[35,40]
2. *Intentionally two-staged transsphenoidal operations* for large suprasellar nonfunctioning pituitary adenomas,[41] performed to avoid a brisk diencephalic decompression and to favor a more extensive removal of the lesion after descent in the sella following the first procedure, could be handled with more ease by means of FEPS for the reasons already mentioned or deserved just to giant adenomas and could be better tolerated by the patient.
3. Without entering the controversy on the best *treatment for PRL-secreting microadenomas*, if medical or surgical, it is important to have an endocrino-neurosurgical team to offer a patient the chance of the best long-term medical treatment and an efficacious and well-tolerated surgical approach. A more articulate therapeutic approach for people harboring an MR well-demarcated microadenoma,[42] offering an easy possibility of avoiding, through surgery, years of treatment, has to be accorded and FEPS, even more than classic transsphenoidal surgery, fits this goal. This endoscopic endonasal approach can be obviously used in macroprolactinomas, also as secondary therapy when medical treatment is ineffective or not tolerated at effective doses, or as emergency treatment for acute pituitary apoplexy, with the aim of debulking the tumor and relieve the optic chiasm.

CONCLUSIONS

The preliminary results of the present study do not allow any definitive conclusions, because of the small series of patients and the necessarily short follow-up. On the other hand, previous valuable studies with statistical significance on a cross section of neurosurgeons in the United States[31] demand 200–500 transsphenoidal operations of a single surgeon to obtain a decreased incidence of morbidity and mortality. However, minimally invasive pituitary endoscopic neurosurgery is now a standard technique, which permits a direct look into the surgical anatomy, with less surgical trauma: it requires previous experience with microneurosurgery and in-depth anatomical knowledge. Early surgical results are at least equivalent to those of standard transsphenoidal procedures, with excellent postoperative course and minimal immediate respiratory difficulties. FEPS appears to be as a minimally traumatic surgery, in respect to inner nose and sellar content. Another relevant aspect which favors the development of FEPS is the economical trend of medicine towards the increase of day-hospital and out-patient treatments, minimizing the periods of prolonged hospital stay. FEPS seems a promising approach in keeping with present need.

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REVIEWER'S COMMENTS

This manuscript by Cappabianca and colleagues addresses a growing trend in pituitary surgery of doing the operation endoscopically through one nostril. Although the neurosurgeon must give up binocular vision through the microscope to use this technique, the ability to use angled telescopes more than compensates for this. In addition, the magnification that can be achieved with an endoscope closer to the tumor also gives a better field of vision. Finally, the upper reaches of these tumors can now be visualized while they are being dissected so that a better and more complete tumor removal can be obtained.

Perhaps most importantly, with this technique there is a much greater respect for the nose and its tissues. Patients afterwards heal much quicker, have less pain, and have a lower incidence of septal perforation and sinus disease.

I applaud Dr. Cappabianca and his colleagues for preparing this manuscript, and I would predict that many other centers will be experiencing the same success with this technique.

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