Endoscopic endonasal transsphenoidal surgery: predictors for disease control in a consecutive series of pituitary adenomas

Mostafa Ismail[a,c], Balegh Abdelhak[c], Jean D'Haens[b], Olaf Michel[a]

[a]Departments of Otorhinolaryngology, [b]Neurosurgery, University Hospital Brussels, Vrije Universiteit Brussel, Brussels, Belgium, [c]Department of Otorhinolaryngology, Minia University Hospital, Minia University, Minia, Egypt

Correspondence to Mostafa Ismail, MD, Universitair Ziekenhuis Brussel Campus, Jette Laarbeeklaan 101, 1090 Brussels, Belgium Tel: + +32 483 298 989; fax: +32 247 76880; e-mail: mostafaismail3730@yahoo.com

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Background
Endoscopic endonasal transsphenoidal surgery for pituitary lesions has been predestined and evolved since its incipient description. However, tumour size and extrasellar extensions of pituitary adenomas remain a challenge for disease control (DC) after surgery. This study was conducted to evaluate the predictors that determine the early outcome in a consecutive series of pituitary adenomas operated using an endoscopic transsphenoidal approach.

Materials and methods
Sixty-five consecutive pituitary adenomas presenting over a 36-month period subjected to excision through an entirely endoscopic transsphenoidal approach were reviewed. DC, based on the extent of tumour resection and endocrinological remission, was evaluated according to the recent radiological and hormonal consensus criteria.

Results
Of 65 pituitary adenomas operated, 24 were endocrinally nonfunctioning and 41 were functioning adenomas. The follow-up duration ranged from 3 to 33 months. The overall DC was 67.7% as measured using total tumour resection and endocrinal cure. Cavernous sinus invasion, suprasellar extension and revision surgery negatively influenced DC of pituitary adenomas. Postoperative complications related to surgical resection of adenomas were seen in 12 cases (18.5%) – mainly, cerebrospinal fluid leakage, anterior pituitary insufficiency, and diabetes insipidus.

Conclusion
This study reports standards for DC in a short follow-up series of purely endoscopic pituitary surgeries and identifies pituitary lesions associated with preoperative predictors that can influence postoperative outcome. These results authenticate the efficacy and safety of endoscopic endonasal transsphenoidal surgery in the treatment of pituitary adenomas, providing favourable DC for both functioning and nonfunctioning pituitary adenomas.

keywords:
disease control

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Introduction

Transsphenoidal surgery is the most widely used surgical approach in the treatment of pituitary tumours since the 1960s due to its adequate surgical outcome [1]. In the early 1990s, the endoscope was introduced to pituitary surgery [2,3] as a collaboration between otolaryngologists and neurosurgeons [4–8]. The use of endoscope supported by the modern improvements in diagnostic imaging has expanded this minimally invasive approach, providing accuracy and safety [9].

The tendency of pituitary macroadenomas for extrasellar extension through the diaphragm sellae into the suprasellar cistern or into the cavernous sinus [10] makes total resection of these tumours challenging [9]. With evolution of the endoscopic endonasal technique supported by intraoperative image guidance, expanded approaches permit a safer and more radical resection of the pituitary adenomas previously considered challenging [11].

Recently, reports were published on preoperative predictors for disease control (DC) based on the extent of tumour resection and endocrinological remission after endoscopic surgical procedures [10–14]. The purpose of current study was to validate the short-term effectiveness of the endoscopic endonasal approach as regards DC in a consecutive series of functioning (FPA) and nonfunctioning pituitary adenomas (NFPAs), with a specific focus on the preoperative predictors for total

resection, endocrinological remission and occurrence of postoperative complications.

Materials and methods

Patient criteria

A consecutive series of 65 pituitary adenoma patients, 36 men and 29 women (age 12–85 years; mean 51±17 years), underwent endoscopic endonasal transsphenoidal surgery (EETS) between May 2012 and 2015 at the University Hospital (Vrije Universiteit Brussel), which was performed by a neurosurgeon (J. D.). The ear, nose and throat (ENT) surgeon (M.I.) was present in all operations to analyse workflow and for documentation. Follow-up (3–33 months) was partially conducted in a prospective manner, covering the period from February 2014 to May 2015 (i.e. 16 months); otherwise, it was retrospective. The Institutional Review Board of The University Hospital of Vrije Universiteit Brussels approved this study.

Surgical technique

In all patients undergoing EETS, rigid endoscopes 300 mm in length and 4 mm in diameter (Olympus, Hamburg, Germany) with angled lenses of 0°, 30° and 70° were used for visualization. A pneumatically powered holder with smooth control of the joints (Aesculap, Tuttlingen, Germany) facilitated fixation of the endoscope and made an instant repositioning possible to manipulate the necessary surgical instruments. This was similar to the technique with the microscope but with a distinct panoramic view, as described by D'Haens *et al.* [15].

A single-nostril approach was performed using the side contralateral to the greatest into four gradesextension of the tumour. The posterior part of the nasal septum was detached from the sphenoid rostrum and pushed towards the contralateral side before a wide bilateral anterior sphenoidotomy was performed using a high-speed drill. Once inside the sphenoid sinus, a C-arm fluoroscope and an image-guided surgery system were used for accurate anatomical orientation.

After exposing the dura, a cross-shaped incision was performed. Adenomas were removed fractionally step by step. Resection of the suprasellar components was achieved following its spontaneous descent into the pituitary fossa, which was facilitated, in most cases, by enhancement of the intracranial venous pressure using Valsalva manoeuvre. For large suprasellar adenomas, extended transsphenoidal approaches are necessary [16]. Laterally extended tumours were dissected from the medial wall of the cavernous sinus. For tumours with cavernous sinus invasion (CSI), an enlarged opening in the dura of the medial wall of the cavernous sinus was made.

After removal of the tumour, the integrity of the diaphragm sellae and arachnoid membrane was controlled for cerebrospinal fluid (CSF) leakage after a Valsalva manoeuvre using angled endoscopes (30° and 70°). In all patients, the sellar floor was reconstructed at the end of surgery using fibrin glue and bone fragments from the sphenoid rostrum. When an intraoperative CSF leakage was evident, a multilayer repair was implemented with intrasellar abdominal fat packing; otherwise, the pituitary fossa was minimally packed using haemostatic materials or left free of packing.

Preoperative and postoperative evaluation

Before surgery, all patients underwent MRI with an imaging protocol, which consisted of 2–3 mm sagittal and coronal planes, T_1-weighted images with and without contrast enhancement and T_2-weighted images. Tumour size, as defined by its maximum diameter, was classified into microadenoma (<10 mm) and macroadenoma (>10 mm). Macroadenomas were further classified into large macroadenomas (≥20 mm) and giant macroadenomas (≥30 mm).

For CSI, the classification of Knosp *et al.* [17] was applied. Lesions classified as Knosp grade 2, 3 and 4 were considered invasive to the cavernous sinus. Suprasellar extension (SSE) was determined according to a modified Hardy's classification [18] into four grades (A–D) according to the degree of SSE above the sellar entrance from 10 mm to more than 30 mm.

Postoperatively, all patients with NFPAs and only patients who failed hormonal cure in FPAs underwent routine MRI to determine the extent of tumour resection at 3, 6 and 12 months following surgery and thereafter once per year, except in the presence of indications for earlier imaging.

All patients underwent preoperative static and dynamic endocrinological evaluations. This pituitary panel included serum cortisol, free thyroxine, thyroid stimulation hormone, adrenocorticotrophic-stimulating hormone, growth hormone (GH) and insulin-like growth factor-1, prolactin, luteinizing hormone and follicle-stimulating hormone, testosterone (in men) and

estradiol (in women). Pituitary function tests were repeated postoperatively at regular intervals on an individual basis depending on the type of pituitary adenoma and patient's clinical status.

All patients were subjected to preoperative and postoperative ophthalmological examination of visual acuity and visual field and a complete neurologic examination. Regular nasal endoscopic examination was carried out by ENT surgeons (M.I. and O.M.) to evaluate the state of the nasal cavity and paranasal sinuses.

Disease control

The aim of surgery was to achieve complete removal of tumours with preservation of pituitary function. Therefore, DC was defined as a total resection of the tumour in NFPAs and as an evidence of endocrinological remission with clinical control in FPAs.

In NFPAs, total tumour resection was considered when the surgeon's intraoperative assessment and the postoperative imaging revealed no residual tumour. Extent of tumour resection was classified as gross total resection (GTR), subtotal resection (STR) when more than 80% of the tumour was resected and as partial resection when less than 80% of the tumour was resected [19]. Residual tumour was classified according to its location as follows: intrasellar, suprasellar, intracavernous or combined [cavernous/suprasellar (C/S)].

The criteria for acromegaly control were normalization of insulin-like growth factor-1 as adjusted for sex and age and suppression of the nadir GH level (<1 μg/l) after oral glucose tolerance test, at least 6 weeks postoperatively [20,21], and improvement in clinical features of acromegaly, particularly soft tissue swelling, hyperhidrosis and sleep apnoea [22]. The criteria for Cushing's DC were normalization of an early morning cortisol level and a 24-hour urinary free cortisol along with an overnight low-dose dexamethasone inhibition test (morning serum cortisol level<18 μg/l) associated with resolution of clinical stigmata [23,24]. Prolactinomas were considered under control when serum prolactin checked at least 6 weeks after surgery was less than 20 ng/ml. All data were obtained from the Department of Endocrinology (Head: Professor Velkeniers).

Statistical analysis

The maximum tumour diameter in patients with controlled and noncontrolled disease as well as in patients with and without postoperative complication was assessed using the Mann–Whitney–Wilcoxon (MWW) test. Using univariate logistic regression analysis, the effect of maximum tumour diameter (microadenoma or macroadenoma), CSI, SSE and revision surgery on DC and the occurrence of postoperative complication was evaluated. A multivariate logistic regression analysis was used to evaluate the effect of combination of all previous factors on DC and the occurrence of postoperative complications. A P value less than 0.05 was considered statistically significant. All data were analysed using statistical package of social sciences, version 20.0 for Microsoft Windows 7 (SPSS Inc., Chicago, Illinois, USA).

Results

General preoperative analysis

A total of 65 patients underwent pure EETS for pituitary adenoma within a 36-month period. Two-thirds of patients (n=41) presented with hormonal overproduction. GH-secreting adenomas were the most common (46.3%). Surgical resection was the first-line treatment in GH-secreting and adrenocorticotrophic-stimulating hormone-secreting adenomas, whereas it was indicated in prolactinomas with failed or nontolerable medical therapy. In NFPAs (n=24), surgical resection was indicated in the presence of headache, visual deficits or impaired pituitary function (Table 1).

Headache and visual deficits were documented in 17 (26.2%) and 11 (16.9%) patients, respectively. In patients with visual deficits, seven patients presented with decreased visual acuity and 10 patients presented with temporal hemianopia; in the majority of patients it was bilateral. Although the pituitary–hypothalamic axis was intact in 67.7% of patients, panhypopituitarism, hypogonadism, hypothyroidism or secondary hyperprolactinaemia were documented in 21 patients. Because of residual tumour or recurrence causing persistent mass effect or excess hormonal production symptoms, seven (10.8%) patients were treated with revision surgery.

Before surgery, MRI revealed macroadenoma in the majority of patients (n=47, 72.3%), with a mean diameter of 21 mm (range: 11–40 mm). A total of 25 macroadenomas had a maximum diameter of 20 mm or greater (large macroadenomas), and seven of them were 30 mm or greater (giant macroadenomas). As regards CSI, patients were divided into two groups: cavernous sinus without invasion (Knosp grade 0, 1) (n=57) and

Table 1 Summary of preoperative characteristics in all patients

	Total (*n*=65) [*n* (%)]	NFPA (*n*=24) [*n* (%)]	GH (*n*=19) [*n* (%)]	ACTH (*n*=10) [*n* (%)]	PRL (*n*=12) [*n* (%)]
Preoperative symptoms					
Headache	17 (26.2)	8 (33.3)	5 (26.3)	2 (20)	2 (16.7)
Visual loss	7 (10.8)	6 (25)	–	–	1 (8.3)
Diplopia	10 (15.4)	9 (37.5)	–	–	1 (8.3)
Impaired pituitary function	21 (32.3)	16 (66.7)	1 (5.3)	–	4 (33.3)
Recurrence	7 (10.8)	4 (16.7)	–	1 (10)	2 (16.7)
Preoperative examination					
Ophthalmologic					
Visual field defect	10 (15.4)	9 (37.5)	–	–	1 (8.3)
Decreased visual acuity	7 (10.8)	6 (25)	–	–	1 (8.3)
Endocrinological					
Panhypopituitarism	7 (10.8)	6 (9.2)	–	–	1 (8.3)
Partial hypopituitarism	12 (18.5)	8 (12.3)	1 (5.3)	–	3 (25)
Secondary HPRL	4 (6.1)	4 (6.1)	–	–	–
Preoperative radiology					
Microadenoma (<10 mm)	18 (27.7)	–	5 (26.3)	7 (70)	6 (50)
Macroadenoma (>10 mm)	47 (72.3)	24 (100)	14 (73.7)	3 (30)	6 (50)
Large adenoma (≥20 mm)	25 (38.5)	13 (54.2)	7 (36.8)	1 (10)	4 (33.3)
Giant adenoma (≥30 mm)	7 (10.8)	4 (16.7)	–	–	3 (25)
Cavernous sinus invasion	18 (27.7)	6 (9.2)	7 (36.8)	1 (10)	4 (33.3)
Suprasellar extension	30 (46.1)	19 (79.2)	5 (26.3)	2 (20)	4 (33.3)

ACTH, adrenocorticotrophic-stimulating hormone; GH, growth hormone; HPRL, hyperprolactinemia; NFPA, nonfunctioning pituitary adenomas; PRL, prolactin.

Table 2 General surgical outcome for the whole series

Outcome	*n* (%)
Total DC	44 (67.7)
DC for microadenomas	17 (94.4)
DC for macroadenomas	27 (57.4)
For large adenomas	9 (36)
For giant adenomas	0
Cavernous sinus invasion	
DC	5 (27.8)
GTR	7 (38.9)
Suprasellar extension	
DC	12 (30)
GTR	21 (70)
Revision surgery	
DC	2 (28.6)

DC, disease control; GTR, gross total resection.

cavernous sinus with invasion (Knosp grade 2, 3, 4) (*n*=18) (27.7%) (Fig. 1). SSE was present in 30 patients (46.1%), which ranged from 10 to 50 mm above the sellar entrance (Fig. 2).

Postoperative disease control

A total 44 patients (67.7%) achieved complete DC. The rate of DC was 94.4% for microadenomas, whereas it was 57.4% for macroadenomas. DC was more favourable for macroadenomas less than 20 mm (81.8%) than that for large and giant macroadenomas (≥20 mm) (36%) (P≤0.001). According to the MWW test, statistically significantly smaller adenomas were recorded in patients with controlled disease compared with those with an uncontrolled one (12.9 vs. 25.5 mm mean maximum tumour diameter, respectively; P<0.001) (Fig. 3a and Table 2).

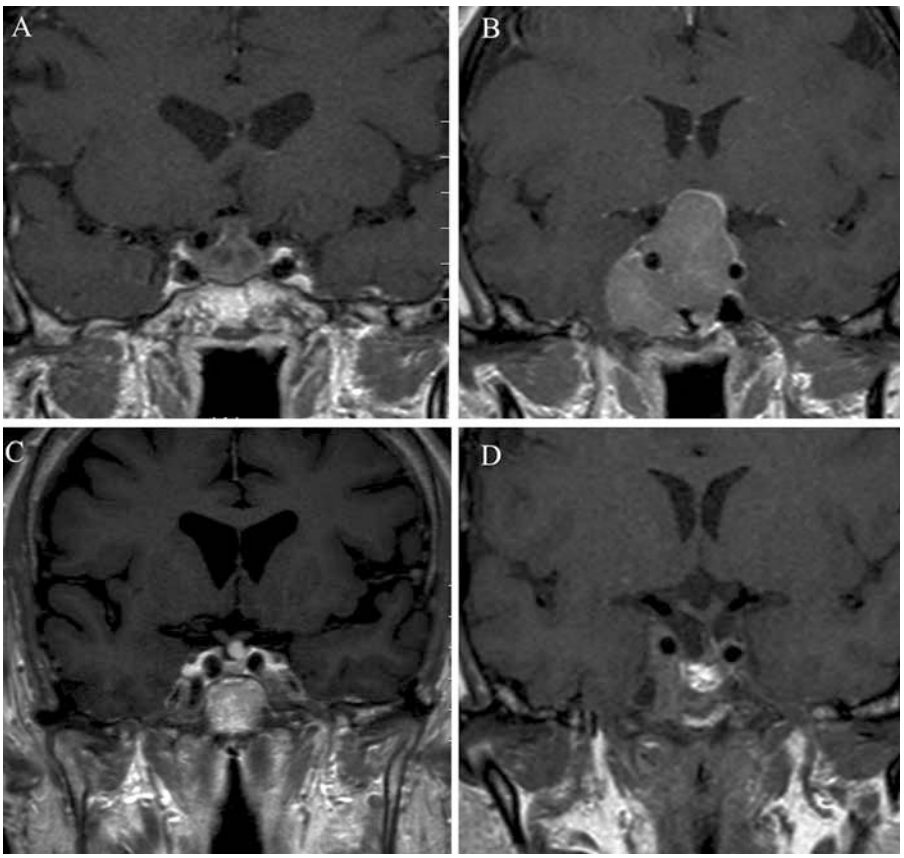
For pituitary adenomas without extrasellar extension nor revision surgery (*n*=27), complete DC was achieved in all patients but one. Once pituitary adenomas showed combined CSI and SSE (C/S) (*n*=13, 20%), the rate of DC declined to 7.7% with intracavernous (*n*=9), suprasellar (*n*=2) or combined C/S (*n*=1) residuals. A difference between DC and GTR was recorded for adenomas with CSI (27.8 vs. 38.9%) and for tumours with SSE (30 vs. 70%) (Table 2).

Seven of total 11 patients with preoperative visual deficits had a good visual outcome (normalized vision, *n*=4; improved vision, *n*=3), whereas it remained unchanged in four patients. Neither visual deterioration nor new visual complaints were recorded postoperatively in our series.

Nonfunctioning pituitary adenomas

According to the first postoperative MRI, GTR with no residual tumour was recorded in 15 patients (62.5%). All patients had macroadenomas with a mean maximum diameter of 22 mm (range: 12–38 mm). Patients with

Figure 1



Coronal T_1-enhanced MRIs of two cases with pituitary macroadenomas. (a) Preoperative CSI; Knosp 2 and SSE; grade A. (b) preoperative CSI; Knosp 4 and SSE; grade B. (c) Postoperative GTR for both CSI and SSE. (d) Postoperative STR with right intracavernous residual. CSI, cavernous sinus invasion; GTR, gross total resection; SSE, suprasellar extension.

Table 3 Surgical outcome for nonfunctioning pituitary adenomas

Outcome	*n* (%)
Total DC	15 (62.5)
DC for microadenomas	–
DC for macroadenomas	15 (62.5)
For large adenomas	6 (46.1)
For giant adenomas	0
Cavernous sinus invasion	
DC	2 (33.3)
GTR	3 (50)
Suprasellar extension	
DC	11 (57.9)
GTR	14 (73.7)
Revision surgery	
DC	1 (25)

DC, disease control; GTR, gross total resection.

controlled disease had statistically significantly smaller adenomas compared with those with an uncontrolled disease, according to the MWW test, (18.5 vs. 27.4 mm mean maximum tumour diameter; P=0.013) (Fig. 3b and Table 3).

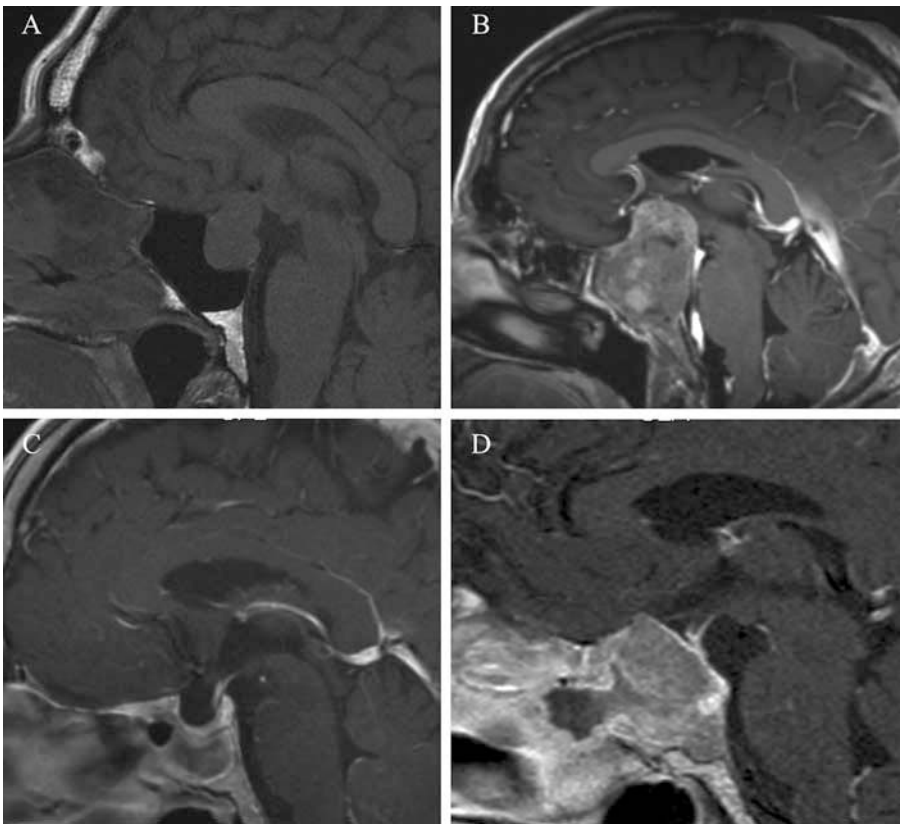
Incomplete tumour resection was recorded in nine cases; four cases had combined CSI and SSE (C/S). Resection was subtotal (>80%) in five cases and partial (<80%) in four cases. Only one case had intrasellar residual tumour due to fibrous recurrent adenoma with difficult surgical resection.

Preoperative impaired pituitary–hypothalamic axis was documented in two-thirds of NFPA patients (n=16, 66.7%). All patients with preoperative secondary hyperprolactinaemia (n=4) normalized after surgery. All but one with preoperative panhypopituitarism (n=6) showed positive postoperative endocrinological outcome (normalized n=1 and improved n=4). Partial hypopituitarism was normalized or improved equally in six patients, whereas it remained unchanged in one patient and worsened in another one.

Functioning pituitary adenomas

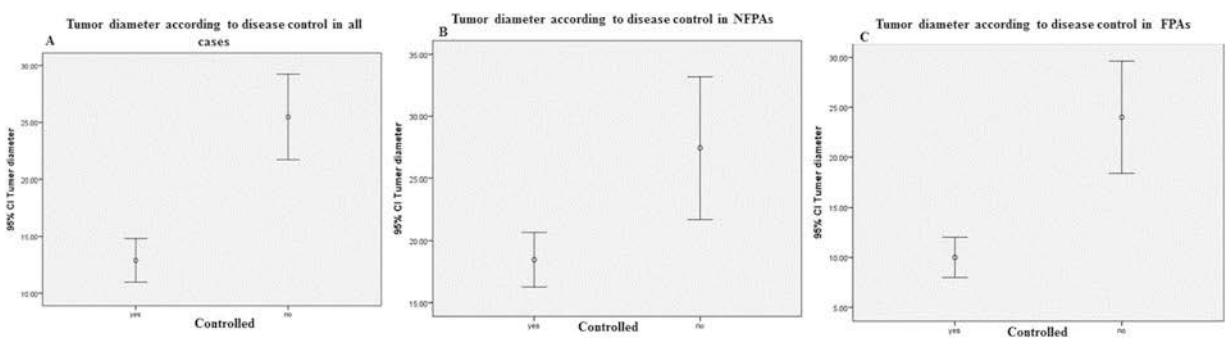
A total of 29 patients (70.7%) had clinical and endocrinological remission based on the criteria

Figure 2



Sagittal T_1-enhanced MRIs of two cases with pituitary macroadenomas. (a), (b) Preoperative suprasellar extension (grades B and D, respectively). (c) Postoperative gross total resection with no residual tumour. (d) Postoperative partial resection with initial descent of the suprasellar residual into the sellar plane.

Figure 3



Association of tumour diameter with disease control for (a) all pituitary adenoma cases, (b) nonfunctioning adenomas and (c) functioning adenomas.

described in the Materials and methods section. Functioning adenomas were categorized into microadenomas (n=18, 43.9%) and macroadenomas (n=23, 56.1%), with a mean maximum diameter of 14 mm (range: 4–40 mm). According to the MWW test, patients with clinical and endocrinological remission had statistically significantly smaller adenomas compared with those with failed remission (mean maximum tumour diameter 10 vs. 24 mm; P<0.001) (Fig. 3c and Table 4).

All cases with combined CSI and SSE (n=8) failed to achieve endocrinological remission. There were six cases of intracavernous residual tumour, one case of suprasellar residual tumour and one case of combined tumour (C/S). A difference between DC and GTR was recorded for all types of FPAs with either CSI or SSE (Table 4).

From a total of five patients with preoperative anterior pituitary deficiency, three patients showed good postoperative endocrinal control (n=1, normalized;

Table 4 Surgical outcome for functioning pituitary adenomas

Outcome	GH [*n* (%)]	ACTH [*n* (%)]	PRL [*n* (%)]
Total DC	13 (68.4)	8 (80)	8 (66.7)
DC for microadenomas	5 (100)	6 (85.7)	6 (100)
DC for macroadenomas	8 (57.1)	2 (66.7)	2 (33.3)
For large adenomas	3 (42.8)	0	0
For giant adenomas	–	–	0
Cavernous sinus invasion			
DC	3 (42.8)	0	0
GTR	4 (57.1)	0	0
Suprasellar extension			
DC	0	1 (50)	0
GTR	2 (40)	2 (100)	3 (75)
Revision surgery			
DC	–	1 (100)	0

ACTH, adrenocorticotrophic-stimulating hormone; DC, disease control; GH, growth hormone; GTR, gross total resection; PRL, prolactin.

Table 5 Preoperative predictors for disease control in 65 pituitary adenoma patients

	Univariate analysis			Multivariate analysis		
	OR	*P* value	95% CI	OR	*P* value	95% CI
Tumor diameter	12.593	0.018*	1.54–102.6	0.498	0.652	0.024–10.296
Suprasellar extension	16	<0.001*	3.9–64.3	12.685	0.005*	2.15–74.6
CS invasion	12.675	<0.001*	3.5–45.7	23.790	0.005*	2.6–218
Revision surgery	6.56	0.034*	1.15–37.3	12.702	0.040*	1.12–143.2

CI, confidence interval; CS, cavernous sinus; OR, odds ratio.
*Significant difference ($P \leq 0.05$).

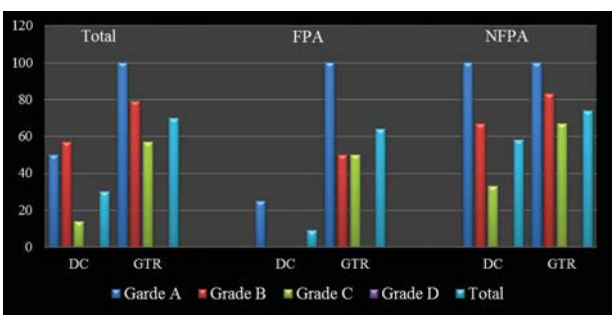
n=2, improved), whereas two patients showed persistent panhypopituitarism in one and hypogonadism in the other. In one patient with preoperative visual deficits, the vision remained unchanged postoperatively.

Preoperative predictors for disease control

According to univariate logistic regression analysis, adenoma maximum diameter greater than 10 mm, SSE, CSI and revision surgery were identified as negative predictors for DC. On combining these significant predictors in a multivariate logistic regression analysis, SSE, CSI and revision surgery remained significant negative predictors for DC, whereas adenoma maximum diameter had no statistically significant relationship with DC (Table 5).

Pituitary adenomas without extrasellar extension nor revision surgery (*n*=27) had significantly favourable DC compared with others with either isolated or combined preoperative negative predictors ($P<0.001$). We reported in our series 17 adenomas with isolated SSE, five with isolated CSI and 13 with combined C/S. There were seven cases of recurrent or residual adenomas and four cases of extrasellar extension.

Figure 4



Percentage of disease control and gross total resection according to suprasellar extension grading.

For adenomas with SSE, GTR of the suprasellar component was achieved in all adenomas (100%) in which tumour height was 10 mm or less above sellar entrance. It was 71.4% for adenomas with height ranging between 10 and 30 mm. This was not as similar as DC yielding on total resection of the whole tumour and endocrinological remission, due to presence of intracavernous residual in 10 cases. None of the grade D adenomas (>30 mm height above sellar entrance) achieved either DC or GTR (Fig. 4, Table 6).

Table 6 Surgical outcome of pituitary adenomas with suprasellar extension

	Total (*n*=30)	NFPA (*n*=19)	GH (*n*=5)	ACTH (*n*=2)	PRL (*n*=4)
DC	12	11	0	1	0
Grade A	3/6	2/2	0/2	1/2	–
Grade B	8/14	8/12	0/1	–	0/1
Grade C	1/7	1/3	0/2	–	0/2
Grade D	0/3	0/2	–	–	0/1
GTR	21	14	2	2	3
Grade A	6/6	2/2	2/2	2/2	–
Grade B	11/14	10/12	0/1	–	1/1
Grade C	4/7	2/3	0/2	–	2/2
Grade D	0/3	0/2	–	–	0/1

ACTH, adrenocorticotrophic-stimulating hormone; DC, disease control; GH, growth hormone; GTR, gross total resection; NFPA, nonfunctioning pituitary adenoma; PRL, prolactin.

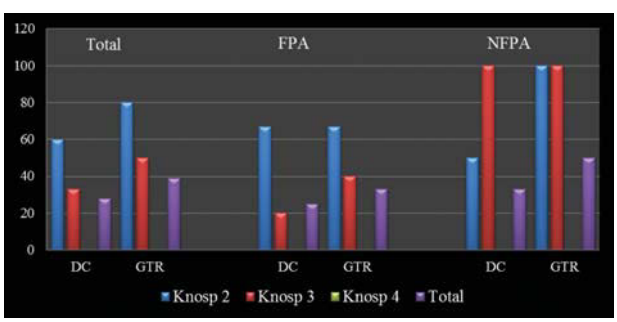
Table 7 Surgical outcome of pituitary adenomas with cavernous sinus invasion

	Total (*n*=18)	NFPA (*n*=6)	GH (*n*=7)	ACTH (*n*=1)	PRL (*n*=4)
DC	5	2	3	0	0
Knosp 2	3/5	1/2	2/3	–	–
Knosp 3	2/6	1/1	1/2	0/1	0/2
Knosp 4	0/7	0/3	0/2	–	0/2
GTR	7	3	4	0	0
Knosp 2	4/5	2/2	2/3	–	–
Knosp 3	3/6	1/1	2/2	0/1	0/2
Knosp 4	0/7	0/3	0/2	–	0/2

ACTH, adrenocorticotrophic-stimulating hormone; DC, disease control; GH, growth hormone; GTR, gross total resection; NFPA, nonfunctioning pituitary adenoma; PRL, prolactin.

Despite the documented difference between DC and GTR for adenomas with CSI, both of them were better in Knosp grade 2 than in Knosp grade 3, except for nonfunctioning adenomas. DC for NFPAs with CSI, defined as total resection of the whole tumour, was better in Knosp grade 3 than in Knosp grade 2 (100 vs. 50%), due to the presence of a large suprasellar residual tumour in one case with Knosp grade 2. None of the Knosp grade 4 adenomas achieved total resection or DC (Fig. 5, Table 7).

Figure 5



Percentage of disease control and gross total resection according to Knosp grading of cavernous sinus invasion.

Seven cases with revision surgery were recorded in our series. Two cases showed isolated intrasellar adenoma, whereas five cases showed extrasellar extension [SSE (*n*=2), CSI (*n*=1) and combined C/S (*n*=2)]. DC was achieved in only two cases (28.6%): one was intrasellar adenoma and the other with intracavernous invasion.

Postoperative complication

Clinically identifiable postoperative CSF leakage was recorded in three cases (4.6%). All leaks were successfully controlled with 4 days lumbar drainage. One case of postoperative mortality due to subdural haemorrhage was recorded. No cases with postoperative intracranial infection occurred in this series. After a regular ENT checkup, one case with postoperative sphenoid sinusitis was documented, which was managed with medications. However, no cases of severe postoperative epistaxis or mucocele formation were documented in our series.

Postoperative diabetes insipidus was observed in five patients. All of them had only transient dysfunction, except for one patient who developed permanent dysfunction requiring medical therapy. Postoperative hypopituitarism occurred in four patients, persistent secondary adrenal insufficiency along with hypogonadism in two patients, initial hypothyroidism in another patient and postoperative panhypopituitarism in only one patient.

Postoperative complications related to surgical resection of the tumour were recorded in 12 patients (18.5%). Notably, all patients who suffered from postoperative diabetes insipidus had no preoperative negative predictors. In cases with CSF leak, subdural hemorrhage and all cases but one with hypopituitarism; one or more of the preoperative

Table 8 Preoperative predictors for development of postoperative complications in 65 pituitary adenoma patients

	Univariate analysis			Multivariate analysis		
	OR	*P* value	95% CI	OR	*P* value	95% CI
Tumour diameter	2.2	0.238	0.59–8.12	6.23	0.123	0.61–63.8
Suprasellar extension	0.828	0.767	0.236–2.9	0.916	0.918	0.173–4.9
CS invasion	1.2	0.818	0.28–4.98	0.252	0.224	0.027–2.3
Revision surgery	1.4	0.764	0.153–12.9	1.288	0.827	0.133–12.51

CI, confidence interval; CS, cavernous sinus; OR, odds ratio.
*Significant difference ($P \leq 0.05$).

negative predictors were recorded. According to univariate and multivariant regression analysis, the previously evaluated predictors for DC, such as tumour maximum diameter, CSI, SSE and revision surgery had no statistically significant association with the development of postoperative complications (Table 8).

Discussion

The transsphenoidal surgery has become a standard in the treatment of intrasellar tumours since more than three decades [9,25–27]. The first use of endonasal endoscopy for the removal of pituitary adenomas was described by Jankowski *et al.* [5] in the 1990s. Subsequently, the endoscopic transsphenoidal technique has been perfected and popularized by Jho and Carrau [28], Cappabianca *et al.* [8] and De Divitiis *et al.* [29].

Because of the tendency of pituitary macroadenomas for extrasellar extension [10], the endoscopic approach offers an advantage in such challenging adenomas with SSE or CSI [11]. This has been provided by its ability to achieve panoramic and angled view when compared with the narrow corridor of the microscopic transsphenoidal approach.

In the current study, we present our surgical outcome following EETS in a consecutive series of pituitary adenomas, with a specific focus on the preoperative predictors for DC based on GTR in NFPA and endocrinological remission in FPA. Our results reported total DC in 67.7% of patients comparable to that reported in the other endoscopic series, with DC ranging from 66.1 to 78.9% [11,30–32].

Preoperative predictors for disease control

Aiming to predict the likelihood for DC following EETS in pituitary adenomas, the effects of maximum tumour maximum diameter, SSE, CSI and revision surgery on postoperative DC were evaluated. These preoperative tumour features have been consistently reported to represent a surgical challenge for total resection and DC [10–14,33]. After a multivariate analysis, three main preoperative predictors were identified to negatively influence DC, in our series: SSE, CSI and revision surgery.

Although patients with controlled disease, in our series, had statistically significantly smaller adenomas compared with those with an uncontrolled disease, maximum tumour diameter was not significantly identified as a preoperative predictor for DC in multivariate analysis (odds ratio 0.498; 95% confidence interval 0.024–10.296; P=0.652). This may be ascribed to using a cutoff of 1 cm tumour diameter, in our series, to define borderline between small and large adenomas (microadenomas and macroadenomas). However, using the traditional 3 cm cutoff maximum tumour diameter threshold [34,35] or the recent volume-based definition of a 10 cm^3 threshold [10], it was recorded that adenomas larger than 3 cm in diameter or 10 cm^3 in volume represent significant predictors for resectability with an increase in likelihood for STR [10,33].

SSE of pituitary adenomas was the most significant independent predictor for tumour control. GTR declines with increased SSE of pituitary adenoma [10,36]. This correlation held true, in our series, when analyzing the SSE both individually or in association with other preoperative predictors ($P \leq 0.001$ and ≤ 0.005, respectively).

The major impact of suprasellar tumour extension on surgical outcome was firstly reported by Jefferson as early in 1940 [10,37]. Later on, Hardy classified pituitary adenomas as follows: type-A, bulging into the chiasmatic cisterns; type-B, reaching the floor of the third ventricle; type-C, large tumours growing up to the foramen of Monro; and type-D, extending into the anterior or middle cranial fossa [38]. With the felicitous evolution of diagnostic imaging, Mohr *et al.* [18] reclassified adenomas with SSE as follows: grade A, moderate SSE up to 10 mm; grade B, large SSE up to 20 mm; grade C, very large SSE up to 30 mm; and grade D, huge SSE in excess of 30 mm.

For adenomas with SSE, a difference between DC and GTR was documented; this was due to the fact that GTR depends mainly on the evaluation of the presence of suprasellar residual tumour on postoperative MRI, whereas DC is a complex process that depends mainly on the whole tumour resection for NFPAs and endocrinal remission for FPAs. This also explains the higher rate of DC in grade B compared with grade A for total cases, in our series, with identified intracavernous residuals. As expected, GTR was recorded to be lower with increasing height of suprasellar component above sellar entrance.

Interestingly, in our series, all suprasellar components with a height up to 10 mm (grade A) were completely resected, whereas STR or partial resection was recorded in all adenomas with suprasellar height greater than 30 mm (grade D). Mohr *et al.* [18] and Honegger *et al.* [36] reported increased rate of residual or recurrence in grades C and D of the suprasellar extended adenomas. However, Hofstetter *et al.* [10] and Messerer *et al.* [13] emphasized that using the extended endoscopic transsphenoidal approaches eliminated SSE as an independent predictor of resectability.

CSI is another factor that diminishes resectability and greatly increases the morbidity of surgical treatment [10]. Three decades ago, Wilson [39] modified Hardy's classification, adding type-E, which was defined as tumour extension into cavernous sinus. Thereafter, the classification by Knosp *et al.* [17] was widely validated for grading CSI, by pituitary adenomas, into four grades based on tumour's relation with the carotid lines. Grade 0 and grade 1 lesions are clearly noninvasive, grades 3 and 4 are considered invasive and grade 2 still represents a matter of controversy between studies [13].

In our series, we recorded a 39% rate of GTR in a cohort of 18 pituitary macroadenomas with CSI; the rate of GTR ranged from 20 to 72% in other endoscopic series [10,11,40]. It was reported that the resectability of an adenoma correlated with the Knosp grade [11]. Notably, a rate of 80 versus 50% GTR of the intracavernous component of pituitary adenomas was recorded in Knosp grades 2 and 3, respectively. When the tumour undoubtedly invades the cavernous sinus (grade 4), the tumour removal is always subtotal due to the high risk for damage of cranial nerves lateral to the cavernous carotid artery (internal carotid artery) [11,13]. For this, the Knosp grade 4 adenomas, in our series, were subjected to incomplete resection.

The lower rate of DC (28%) for adenomas with CSI as compared with GTR (39%), in our series, was attributed to the presence of SSE in some cases, which affects DC independent of Knosp grade. This explains the higher rate of total tumour resection in Knosp grade 2 compared with grade 1 in the series of Paluzzi *et al.* [11] and also the lower rate of endocrinological remission (43%) compared with GTR (59%) in the series of Frank *et al.* [31].

Revision surgery in the current series negatively influenced postoperative DC; similar findings have been previously reported [33]. This was proved, in our series, either individually or in association with other preoperative predictors (P=0.034 and 0.04, respectively).

Total resection of recurrent or residual adenomas is technically difficult because of disturbed anatomy or extensive bleeding, which was attributed to adhesions and use of reconstructing materials [33]. Furthermore, postoperative radiotherapy may be performed in patients with residual tumours for stabilizing tumour growth or inducing regression of the adenoma [41,42].

An overall incidence of 18.5% for postoperative complications, which related to surgical resection of pituitary adenomas, was recorded in the current series. This was comparable to the incidence reported in previous endoscopic series, which ranged from 13.6 to 25.2% [30–32]. In our series, none of the previously evaluated predictors for DC, maximum tumour diameter, CSI, SSE and revision surgery, had statistically significant association with development of postoperative complications either individually or in combination. This may be ascribed to the decreasing rate of resection with the higher extrasellar invasion compared with a possible high rate of GTR in adenomas with low extrasellar invasion.

Conclusion

The early outcome of the endoscopic endonasal transsphenoidal resection of pituitary adenomas revealed DC in 67.7% of (n=65) patients. The results of this study underline the efficacy and safety of EETS for pituitary adenomas with the ability to achieve favourable DC for both FPAs and NFPAs with very low morbidity.

Indeed, such adenomas with SSE, CSI and revision surgery are helpful to identify pituitary lesions associated with preoperative predictors that can influence postoperative DC.

Conflicts of interest

There are no conflicts of interest.

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