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ENDOCRINE SURGERY

Microsurgical therapy of pituitary adenomas

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Abstract
Purpose We report the efficacy and safety of transsphenoidal microsurgery in a large and homogeneous cohort of patients with pituitary adenomas (PAs) treated at a single Institute by a single neurosurgeon.
Methods A total of 2145 consecutive patients undergoing first surgery for a PA were included: 795 (37.1%) had a nonfunctioning pituitary adenoma (NFPA), 595 (27.7%) acromegaly, 496 (23.1%) Cushing's disease, 208 (9.7%) a PRL-secreting adenoma, and 51 patients (2.4%) a TSH-secreting adenoma. Remission was achieved when strict hormonal and radiological criteria were met.
Results Early surgical remission was achieved in 66% of acromegalic patients, 79.6% of patients with Cushing's disease, 64.4% of prolactinomas, 74.5% of patients with a TSH-secreting adenoma, and 66.9% of NFPAs. The mean (±SE) follow-up was 60.1 ± 1.3 months. The recurrence-free survival at 10 years was 78.2% in acromegalic patients, 68.1% in prolactinomas, 74.3% in Cushing's disease, 70.3% in TSH-secreting adenomas, and 75.3% in NFPAs. Preoperative hypoadrenalism recovered in 35.3%, hypogonadism in 43.3% and hypothyroidism in 37.4% of patients with impaired function before surgery. The mortality rate was 0.2% and major morbidity 2.1%. New onset hypoadrenalism occurred after surgery in 2.5% of patients at risk, hypogonadism in 4.1%, and hypothyroidism in 1.8%. Permanent diabetes insipidus (DI) occurred in 0.9% of patients.
Conclusions In experienced hands, transsphenoidal microsurgery for PAs achieves remission in most patients with a low complication rate. Pituitary function is preserved in most cases and can recover in more than one-third of patients with preoperative hypopituitarism.

Keywords Pituitary adenomas · Transsphenoidal surgery · Surgical results · Surgical complications.

Introduction

It is generally accepted that most pituitary adenomas (PAs) require treatment to reverse the endocrine hyper-secretion, decompress the nervous structures, control the tumor growth, and preserve the normal pituitary function [1]. At present, the optimal management of PAs may be multimodal, combining surgery, drugs, and radiation therapies [1]. Surgery is considered the first-choice therapy in the majority of cases, except for prolactinomas responsive to dopamine agonists [2]. Other treatments, such as drugs, stereotactic radiosurgery, and radiotherapy play an important role as adjuvant therapy or when surgery is contraindicated due to critical health condition.

The transsphenoidal approach to PAs is the preferred surgical route in most cases and the role of surgeon's experience is of critical importance [3]. Over the past 20 years, the endoscopic technique has been introduced into clinical practice [4–6]. The supposed advantages of endoscopy compared with the microscopic technique are a lower risk of complications and improved efficacy. However, a systematic review of published result of both microsurgical and endoscopic series does not confirm a significant

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difference between the two techniques [7–16] and underlines the higher incidence of some complications after endoscopy [7–16].

In this study, we report the results of microscopic transsphenoidal surgery (TSS) performed by a single pituitary-dedicated neurosurgeon in more than 2000 consecutive patients with PA.

Patients and methods

Patients

Between January 1990 and December 2016, 3040 consecutive patients with PA were operated at the Neurosurgery Department of San Raffaele Institute. In this study, we included the 2145 patients operated for the first time by the senior author (P.M.) only. The sublabial trans-sphenoidal microsurgical technique adopted in all surgical procedures has previously been described in detail elsewhere [2]. The duration of the surgical procedure was in mean 38 min [17].

Seven hundred ninety-five patients had a non-functioning pituitary adenoma (NFPA) and the remaining 1350 had a hormone-secreting pituitary adenoma (HSPA).

Clinical, radiological and visual examinations

Hormonal evaluation and magnetic resonance imaging (MRI), or computed tomography when MRI was contra-indicated (seven cases) were performed in all patients at diagnosis. The maximum tumor diameter was measured on MRI and adenomas were further classified according to tumor size and parasellar invasion [18–20]. Macro-adenomas accounted for 54.6% of HSPAs and 99.5% of NFPAs. Invasiveness into the cavernous sinus was evident in 14.1% of HSPAs and 30.8% of NFPAs (Table 1).

Patients with macroadenoma underwent ophthalmologic evaluation before surgery, 6 months after and then yearly. The visual field was assessed by computerized perimetry and the visual acuity was measured adopting the best correction for refractive disorder, using standard optotypes. Postoperative visual outcomes were classified as improved, worsened or unchanged. After surgery in all patients plasmatic and urinary electrolytes and osmolality are daily evaluated until discharge in fifth–seventh day, in addition to fluid intake and output. Standard histological examination of paraffin-embedded tissue sections and immunocytochemical studies confirmed the diagnosis of PA in all patients.

Postoperative and follow-up data were prospectively collected into an electronic database.

Criteria of remission and recurrence

The commercial assays used for hormone measurements were subjected to several changes over the very long period of the study but the hormone criteria to classify the response to surgery were adjusted, when necessary, to take into account the different sensitivity of the assays. Patients were considered in remission of disease when the following criteria were met:

- Acromegaly: basal or oral glucose tolerance test-suppressed GH below 1 μg/L, as measured by 22K-specific assays, plus age-adjusted and sex-adjusted normalization of elevated IGF-1 level.
- Prolactinoma: normalization of basal prolactin (PRL) level, without dopaminergic therapy for at least 6 months.
- Cushing's disease: hypocortisolism requiring glucocorticoid substitution therapy or normal serum and urinary cortisol levels with suppression of serum cortisol level below 18 ng/mL after an overnight low-dose dexamethasone test.
- Thyroid-stimulating hormone (TSH)-secreting adenoma: normalization of serum TSH, free triiodothyronine, and free thyroxine levels in hyperthyroid patients plus absence of residual disease on postoperative MRI.
- NFPA: absence on the first postoperative MRI, performed 3–6 months after surgery, of residual adenomatous tissue.

Additionally, patients with a HSPA were considered in remission when the above-depicted hormonal criteria were fulfilled for a minimum of 6 months after surgery.

Recurrence of a HSPA was diagnosed in patients with biochemical evidence of hormone hypersecretion after remission, whereas in patients with NFPA recurrence was diagnosed when a new lesion became evident on MRI in patients with a postoperative MRI without any residual tumor.

Surgical complications

The surgical mortality rate included all deaths that occurred within 2 months from TSS or later as a direct consequence of postoperative complication. Medical and surgical complications were counted separately. Complications were grouped into major, minor, hormonal and electrolytes disturbances [21, 22]. Surgical complications included intracranial hemorrhages, cerebrospinal fluid (CSF) rhinorrhea, meningitis, visual worsening, cranial nerves palsy, and oro-rhino-sinusal complications, whereas medical complications were generally linked to anesthesia and/or hospitalization. The surgical and medical morbidity rates were calculated considering all patients who experienced at least one of these complications.

Table 1 Clinical characteristics of 2145 patients operated for pituitary adenoma

Type of adenoma (*n*)	Mean age ± SE years (range)	Female *n*(%)	Macroadenoma *n*(%)	Cavernous sinus invasion *n*(%)[a]	Maximum tumor diameter mm(range)[b]	Giant adenomas *n*(%)[c]
GH-secreting	46.1 ± 0.5	314	477	128	17.7 ± 0.4	12
(595)	(12-74)	(52.8)	(80.2)	(21.5)	(4–72)	(2)
ACTH-secreting	40.1 ± 0.8	390	106	25	8.2 ± 0.3	1
(496)	(6-80)	(79.8)	(21.4)	(5)	(2-40)	(0.2)
PRL-secreting	33 ± 0.8	153	116	26	14.1 ± 0.7	6
(208)	(9-67)	(73.6)	(53.8)	(12.5)	(3-50)	(2.9)
TSH-secreting	42.8 ± 1.8	25	38	12	19.6 ± 1.6	4
(51)	(14-68)	(49)	(74.5)	(23.5)	(3-51)	(7.8)
HSPA	**41.6 ± 0.4**	**882**	**737**	**191**	**13.7 ± 0.3**	**23**
(1350)	**(6-80)**	**(65.3)**	**(54.6)**	**(14.1)**	**(2-72)**	**(1.7)**
NFPA	**54.4 ± 0.5**	**336**	**790**	**245**	**27.6 ± 0.3**	**64**
(795)	**(11-85)**	**(42.3)**	**(99.5)**	**(30.8)**	**(7-80)**	**(8)**

SE standard error, *GH* growth hormone, *PRL* prolactin, *ACTH* adrenocorticotropin, *TSH* thyrotropin, *HSPA* hormone secreting pituitary adenoma, *NFPA* nonfunctioning pituitary adenoma

Bold values indicate the clinical characteristics of HSPA and NFPA

[a] Tumors were considered as invasive into the cavernous sinus when classified as grade 3 or 4 of the Knosp's classification [17]

[b] Maximum tumor diameter was measured on the preoperative MRI

[c] Giant adenoma was considered as a tumor showing a maximum tumor diameter of 4 cm or more

Water and electrolyte disturbances after TSS included permanent diabetes insipidus (DI) and isolated hyponatremia (IHN). Permanent DI was diagnosed when hypotonic polyuria (greater than 30 ml/Kg bodyweight in 24 h) ensued after surgery and lasted for at least 2 months. IHN was defined by postoperative serum sodium level less than 132 mmol/L.

Statistical analysis

Continuous data were expressed as mean ± standard error (SE) and compared with the unpaired Student's *t*-test. Categorical variables were reported as number and/or percentage and were compared with the Pearson's X^2 or Fisher exact test as appropriate. Recurrence-free survival was calculated using the Kaplan–Meier method. Differences of survival between subgroups of patients were tested by the log rank method. Data for patients who were lost at follow-up or died were censored at the date of the last follow-up. A probability value less than 0.05 was considered significant and all reported probability values are two-tailed. All calculations were performed using the statistical package IBM SPSS Statistics, Version 20.

Results

Early and long-term results

Several patients were lost to clinical follow-up or have contraindication to do MRI, so data on efficacy of TSS were available for 2081 of the 2145 patients (97.0%). The overall surgical remission rate was 71.1% (948 of 1335 patients) in HSPAs and 66.9% (499 of 746 patients) in NFPAs. Except for ACTH-secreting adenomas, patients with microadenoma had a better outcome than patients with macroadenoma ($p < 0.0001$; Table 2). The other tumor characteristic that was negatively associated with early favorable surgical outcome was invasiveness into the cavernous sinus ($p < 0.0001$; Table 2). Indeed, invasive tumors had remission rates ranging from 0% in prolactinomas to 36% in Cushing's disease whereas not invasive tumors had a higher probability of remission in all types of PAs.

Most patients noticed improvement of symptoms related to compression of the optic pathway soon after surgery. A preoperative visual defect was present in 477 patients (22.2%) of whom 216 (45.3%) had impairment of visual acuity and the remaining 261 patients (54.7%) had visual defects only. Postoperative improvement was achieved in 425 patients (89.1%). The chance of visual recovery was similar in patients who had defects of visual acuity and in those who had visual field defects (87.1% vs. 90.8%, respectively).

Pituitary function improved after surgery (Table 3). Indeed, recovery of impaired adrenal, thyroid, and gonadal function occurred in 77 of 218 (35.5%), 112 of 299 (37.4%), and 523 of 1208 patients (43.3%), respectively. The chance of recovery of pituitary function was similar in patients with NFPA and in those with HSPA, except for hypogonadism that improved more frequently in the latter group (56.7% in HSPA and 26.7% in NFPAs, $p < 0.001$).

The mean follow-up after surgery was 60.1 ± 1.3 months (6-252). The overall risk of recurrence was 11.8% (59 of

Table 2 Early and late surgical outcome in 2081 patients operated for pituitary adenoma

Type of adenoma	Surgical remission *n* (%)[a]					Mean follow-up months (range)	Recurrence *n* (%)	Time of recurrence months (mean and range)
	Overall	Microadenomas	Macroadenomas	Invasive tumors	Non-invasive tumors			
GH-secreting	383/582	102/115	284/470	18/126	368/459	54.5 ± 2.4	20/383	40.1 ± 2.2
	(66)	**(88.7)**	**(60.4)**	**(14.3)**	**(80.2)**	6-252	**(5.2)**	8-218
ACTH-secreting	393/494	314/388	79/106	9/25	384/469	50.5 ± 2.4	42/392	44.8 ± 2.4
	(79.6)	**(80.9)**	**(74.5)**	**(36)**	**(81.9)**	6-242	**(10.7)**	8-204
PRL-secreting	134/208	78/96	56/112	0/26	134/181	48.2 ± 3.5	19/134	42.8 ± 5.9
	(64.4)	**(81.2)**	**(50)**	**(0)**	**(74)**	6-211	**(14.2)**	7-190
TSH-secreting	38/51	13/14	25/37	2/12	36/39	43.3 ± 8.3	5/38	32.3 ± 7.2
	(74.5)	**(92.8)**	**(67.6)**	**(16.7)**	**(92.3)**	6-242	**(13.1)**	8-200
NFPA	499/746	4/4	488/727	76/232	423/512	76.6 ± 2.3	59/499	60.2 ± 2.4
	(66.9)	**(100)**	**(67.1)**	**(32.7)**	**(82.6)**	6-247	**(11.8)**	9-242

GH growth hormone, *PRL* prolactin, *ACTH* adrenocorticotropin, *TSH* thyrotropin, *HSPA* Hormone secreting pituitary adenoma, *NFPA* nonfunctioning pituitary adenoma

Bold values indicate the percentages

[a] See text for criteria of cure

Table 3 Change of hormonal function and electrolytes disturbances in 2145 patients undergoing surgery for pituitary adenoma

Type of adenoma	Anterior pituitary function—postoperative improvement *n* (%)			Anterior pituitary function—postoperative new onset deficiency *n* (%)			Permanent diabetes insipidus *n* (%)	*Hyponatraemia n (%)*
	Hypoadrenalism	Hypogonadism	Hypothyroidism	Hypoadrenalism	Hypogonadism	Hypothyroidism		
GH-secreting	4/9 (44.4)	135/244 (55.3)	16/22 (72.7)	6/567 (1.1)	5/328 (1.5)	4/502 (0.8)	4/595 (0.6)	17/595 (2.9)
PRL-secreting	2/9 (22.2)	83/166 (50)	6/17 (35.3)	1/199 (0.5)	0/41	1/182 (0.5)	4/208 (1.9)	6/208 (2.9)
ACTH-secreting	–	153/242 (63.2)	20/32 (62.5)	–	4/219 (1.8)	3/424 (0.7)	1/496 (0.2)	43/496 (8.7)
TSH-secreting	0/3	8/16 (50)	–	1/48 (2.1)	0/34 (0)	–	2/51 (3.9)	0
HSPA	**6/21 (42.8)**	**379/668 (56.7)**	**42/71 (59.1)**	**8/814 (0.9)**	**9/622 (1.4)**	**8/1108 (0.7)**	**11/1350 (0.8)**	**66/1299 (5)**
NFPA	**71/197 (36)**	**144/540 (26.7)**	**70/228 (30.7)**	**27/569 (4.7)**	**27/238 (11.3)**	**22/512 (4.3)**	**10/795 (1.2)**	**34/795 (4.3)**
Total	77/218 **(35.3)**	523/1208 **(43.3)**	112/299 **(37.4)**	35/1383 **(2.5)**	36/869 **(4.1)**	30/1620 **(1.8)**	21/2145 **(0.9)**	100/2145 **(4.7)**

GH growth hormone, *PRL* prolactin, *ACTH* adrenocorticotropin hormone, *TSH* thyrotropin hormone, *HSPA* Hormone secreting pituitary adenoma, *NFPA* nonfunctioning pituitary adenoma

Bold values indicate the results about HSPA and NFPA

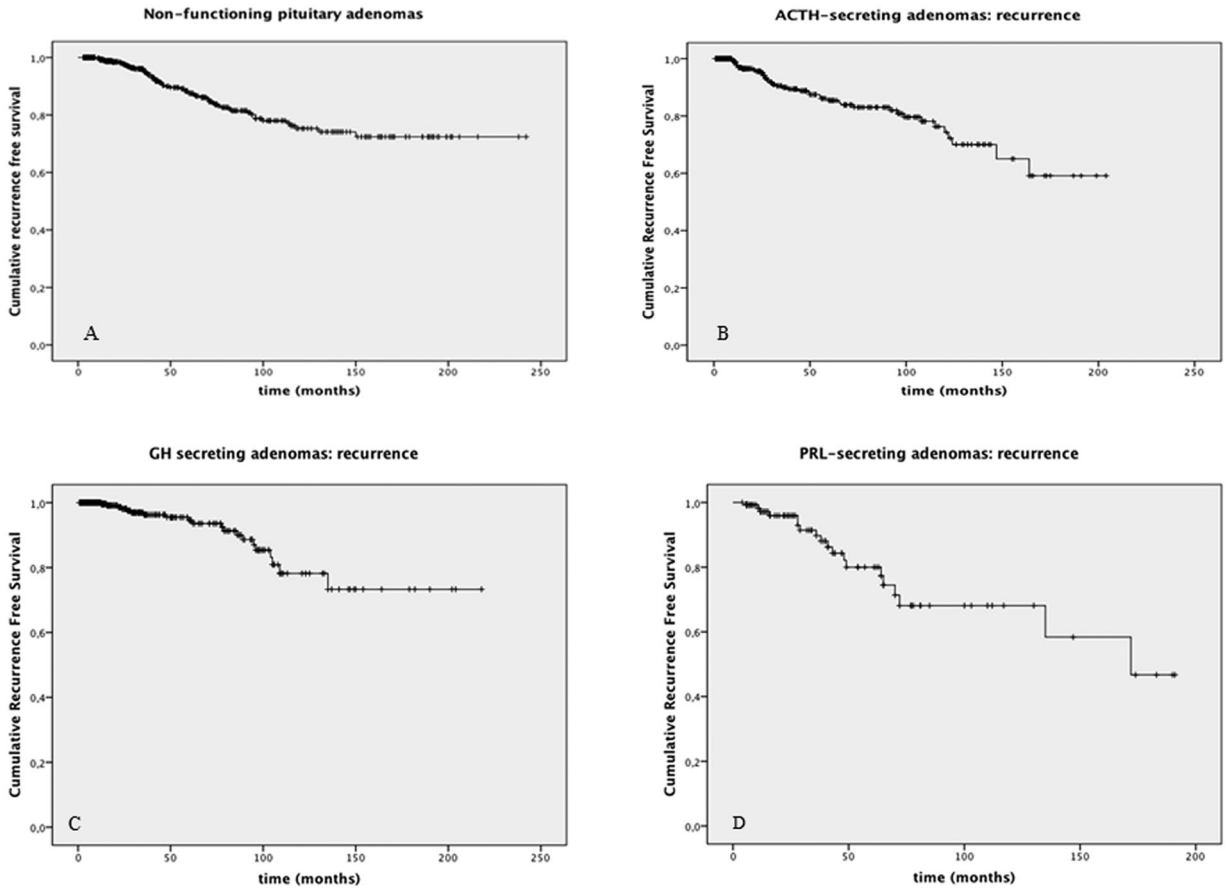

Fig. 1 **a** Cumulative recurrence-free Kaplan–Meier curve in 795 NFPA. At 10 years, the recurrence-free survival is 75.3% (95% confidence interval, 57-79%). **b** ACTH-secreting adenomas ($n = 496$): at 10 years, the recurrence free survival is 74.3% (95% confidence interval, 66-82%). **c** GH-secreting adenomas ($n = 595$): at 10 years, the recurrence-free survival is 78.2% (95% confidence interval, 68-88%). **d** PRL-secreting adenomas ($n = 208$): at 10 years, the recurrence-free survival is 68.1% (95% confidence interval, 54-82%)

499 patients) in NFPA, 10.7% (42 of 392 patients) in Cushing's disease, 5.2% (20 of 383 patients) in acromegaly, 14.2% (19 of 134 patients) in prolactinomas, and 13.1% (5 of 38 patients) in patients with TSH-secreting adenoma. The cumulative recurrence-free survival curves in the various groups of patients are depicted in Fig. 1. At 10 years, the recurrence-free survival was 75.3% (95% CI, 57-79%), 74.3% (95% CI, 66-82%), 78.2% (95% CI, 68-88%), 68.1% (95% CI, 54-82%), and 70.3% (95% CI, 48-100%) in patients with NFPA, Cushing's disease, acromegaly, prolactinoma, and TSH-secreting adenoma, respectively.

Complications

Five deaths occurred postoperatively, accounting for an overall surgical mortality rate of 0.2%. Four deaths occurred in 795 patients with NFPA (0.5%), while the remaining death occurred in the 1350 patients with a HSPA (0.07%). Causes of death were massive pulmonary embolism in a 80-year-old man with NFPA, hemorrhagic infarction of an incompletely resected giant NFPA in a 68-year-old woman, subarachnoid hemorrhage without any artery injury or evidence of vascular malformation at angiography in a 72-year-old man with a giant NFPA, subarachnoid hemorrhage causing vasospasm and severe neurological sequel leading to death 1 year after surgery in a 56-year-old man with NFPA, and multi-organ failure due to a perforated bowel diverticulum in a 75-year-old woman with Cushing's disease.

Table 4 summarizes the complications recorded in our patients. Major surgical complications occurred in 2.1% of the 2145 patients. The risk of experiencing an adverse event was higher in patients with NFPA (3.8%) than in patients with HSPAs (1.0%; $p < 0.01$). Moreover, patients with a major surgical complication were also significantly older than patients without adverse events (52.4 ± 2.6 years vs. 46 ± 0.4 years, respectively; $p < 0.01$) and had a larger maximum tumor diameter (29.5 ± 2.1 mm vs. 18.5 ± 0.2, respectively; $p < 0.001$).

Minor complications occurred in 1,35% of 2145 patients and had a similar incidence in both HSPAs (1%) and NFPAs (1.9%). Age did not influence the frequency of

Table 4 Postoperative complications in 2145 patients operated for pituitary adenoma

Pituitary Adenoma	Total	NFPA	HSPA
n patients	**2145**	**795**	**1350**
Complications	*n* (%)	*n* (%)	*n* (%)
Mortality	5 (0.2)	4 (0.5)	1 (0.07)
Surgical complications			
CSF rhinorrhea requiring surgery	6 (0.27)	3 (0.4)	3 (0.2)
Meningitis	5 (0.2)	5 (0.6)	0
Permanent visual worsening	3 (0.1)	1 (0.1)	2 (0.1)
Transient cranial nerve dysfunction	8 (0.4)	6 (0.7)	2 (0.1)
Sellar Hemorrhage requiring surgery	3 (0.1)	3 (0.4)	0
Intracranial hemorrhage	5 (0.2)	3 (0.4)	2 (0.1)
Carotid artery injury	0	0	0
Oro-rhino-sinusal complications	10 (0.5)	5 (0.6)	5 (0.37)
Medical complications	33 (1.5)	20 (2.5)	13 (0.9)
New onset hypopituitarism[a]	101 (4.7)	76 (9.5)	25 (1.8)
Water and electrolyte disturbances			
DI > 2 months	79 (3.7)	32(4)	47 (3.5)
Hyponatremia	100 (4.7)	34 (4.3)	66 (5)

NFPA nonfunctioning pituitary adenoma, *CSF* cerebrospinal fliud, *DI* diabetes insipidus

Bold values indicate the number of patients

minor complications whereas the maximum tumor diameter was higher in patients with minor complications than in patients without complications (25 ± 2.3 mm vs. 18.5 ± 0.2 mm, respectively; $p = 0.002$).

Endocrine, water balance, and electrolyte complications are reported in Table 3. New onset deficiency of gonadal, adrenal, and thyroid function after surgery occurred in 11.3%, 2.5%, and 1.8% of patients at risk, respectively (Table 3).

Permanent DI occurred in 21 of 2145 patients (0,9%). It was diagnosed in 79 of 2145 patients (Table 3) but spontaneously normalized after a mean follow-up of 4 ± 0.4 months after surgery in 58 cases (range 1–32 months). Postoperative hyponatremia developed in 100 of 2145 patients (4.7%) 6.7 ± 0.3 days after surgery (range 3-30 days). It was more frequent in small tumor (15.2 ± 1.2 mm vs. 19.1 ± 0.2 mm, $p = 0.01$) and ACTH-secreting adenomas ($p < 0.001$, Table 3). Usually postoperative hyponatremia was asymptomatic or associated with nausea, vomiting and headache; only in two cases epileptic seizures occurred. The lowest value was on average 124.8 ± 0.6 mmol/L (range 108–132).

Discussion

It is widely recognized that TSS is an effective and safe therapeutic option in patients with PA [2, 23, 24]. The

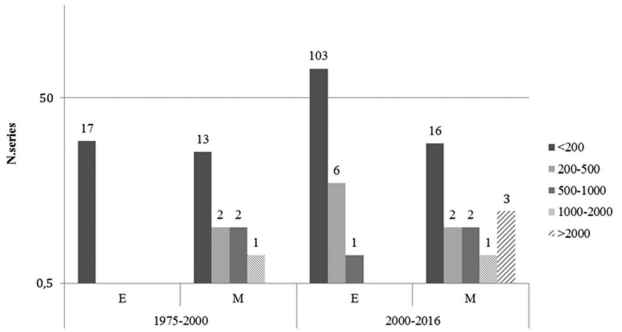

Fig. 2 Distribution of published endoscopic (E) and microsurgical (M) series from 1975 to 2016 (axial logarithmic scale, base 10)

efficacy of pituitary surgery should be ideally evaluated on well-defined criteria of remission, including the outcome 6 months after surgery and the recurrence rate at follow-up in a homogeneous cohort of patients treated by the same neurosurgeon at a single institution. The recent literature on TSS for PAs is dominated by some bias, such as the different surgical techniques, surgery performed by different surgeons in the same series, and unclear or inappropriate criteria of cure. Moreover, the majority of recent series include less than 200 cases, which is the accepted threshold to consider a pituitary surgeon as "experienced" [3]. In the last 16 years, the number of peer reviewed publications reporting small cohort of patients increased dramatically due to the diffusion of pure endoscopic techniques and the extensive collaboration between neurosurgeons and rhinologic surgeons (Fig. 2). Moreover, even the largest endoscopic series present some weakness in the recurrence rate [25–31] and/or criteria of cure [27–29]. At present, there is no evidence in large series and prospective studies that endoscopic TSS is superior to microsurgery, as already confirmed by a comparative study and a systematic review of the literature [9, 10, 12, 17, 32, 33].

One caveat of our study, as well as of any other series spanning the results of several years, is the changing definition of surgical remission and the different assays used to measure hormone concentrations. This problem is particularly evident in the case of acromegaly. To diminish the risk of surgical results misclassification, diagnostic cut-off values where adjusted whenever indicated and all hormonal results have been analyzed by a single endocrinologist (M.L.). Moreover, it has always been our policy to require normalization of hormone secretion for at least 6 months from surgery and not only in the early postoperative period to consider a patient in remission.

In our experience, TSS is an effective treatment for both HSPAs and NFPAs. These results are consistent with those of the largest series reported in literature [2, 24, 34–36]. The remission rates obtained in a recent meta-analysis were: 61.2% in acromegaly, 68.8% in prolactinomas, 71.3% in

Cushing's disease and 47.3% in NFPAs; the rate was significantly lower in the last group [34]. In our series, the type of adenoma was not a prognostic factor, whereas the small size, except in Cushing's disease, and the absence of cavernous sinus invasion were positive prognostic factors for early surgical remission.

Recurrence of disease is one caveat of surgery and may be an important determinant of the long-term outcome and quality of life of patients affected by PAs. For this reason, it is essential that surgical series report not only early but also late results of surgery. Unfortunately the recurrence rates are not reported in any of the largest endoscopic series [24–30]. In our study, the recurrence-free survival rate was slightly higher in prolactinomas than in other types of PAs. The mean time of recurrence in NFPAs was similar to that in HSPAs (60.2 and 56.9 months, respectively; Table 2). In a meta-analysis, the majority of recurrences were reported 1–5 years after surgery, although patients with acromegaly and NFPAs displayed a significant number of recurrences 5–10 years after surgery. In keeping with our data, the highest recurrence rate at follow-up was reported in prolactinomas and NFPAs [34]. The most important predictor for recurrence in HSPAs was the postoperative basal hormone level while in NFPAs age, tumor size, and invasion were found significant in some studies only [37, 38]. Analyses of clinical, radiologic, histologic, immunocytochemical, and ultrastructural features have failed to find out characteristics consistently associated with the risk of recurrence. The morphologic markers of tumor aggressiveness, including pleomorphism, nuclear atypia, increased cellularity, and mitotic activity, did not correlate with the prognosis of PAs [24]. While some authors reported the prognostic significance of Ki-67, others found no significant association between this marker and tumor recurrence [37, 39–41]. In our series, most recurrences were successfully managed by multimodality treatments, such as repeat surgery, drugs, and radiation therapy [42].

Symptomatic improvement of preoperative visual defect is one of the major goals of surgical treatment of PAs. Confirming our previous results in a smaller series of patients [43], around 90% of patients experienced a significant improvement of visual acuity and visual field defects. Similarly, recovery of pituitary function is a clinically meaningful but often unrecognized positive effect of surgical treatment of PAs [43–45]. In particular, Dekkers and coworkers [43] reported that patients with NFPA had improvement of pituitary function in a limited number of cases, which was counterbalanced by worsening of endocrine activity in other patients. In our series, improvement of anterior pituitary insufficiency occurred in more than one third of patients (Table 3). In particular, hypogonadism recovered more frequently in HSPAs than in NFPAs, whereas new onset hormone deficits occurred less frequently (see below). The variability of these results might depend on the different criteria adopted to define hypopituitarism, the use of postoperative radiation therapy and the differences of patients' characteristics in other series.

A critical point of TSS concerns safety. Our series confirms that when surgery is performed by a dedicated pituitary neurosurgeon, the risk of adverse events is very low. The reported mortality and the morbidity rates of TSS for PAs are low [23–25, 28, 30, 31, 35, 36, 46–48]. In our series, the mortality rate was 0.2% with almost all deaths occurring in elderly patients in poor health conditions and/or with a giant tumor, whereas major morbidity was detected in 2.1% of our patients. Confirming previous data from our group, older age, maximum tumor diameter, and NFPAs were risk factors for major adverse events [49]. The incidence of overall CSF leak is reported to occur in 3.8–8.3% of patients [23, 25–31, 35, 36, 47], while, in our series it occurred in 0,5%. Moreover, the reported incidence of CSF leak requiring reoperation is 0.4–6.4%. In our series, only 0.27% of patients required a second transsphenoidal procedure to close the CSF leak. We found a risk of postoperative meningitis of 0.2%, which is at the lower end of the data reported in the literature [3, 21]. These data confirm that our policy to withdraw antibiotic prophylaxis in the postoperative setting [2] does not increase the infectious risk of TSS. There was no carotid injury in any of our patients. In a meta-analysis, the percentage of carotid injury and hemorrhagic complications reported in endoscopic series resulted significantly higher compared with microscopic series [16]. The aggressive extended lateral approach suggested by some authors might explain the higher incidence of this complication in endoscopic series [16]. Considering the minimal probability of cure in truly invasive PAs, the idea to attempt total removal in such cases should be regarded as "naïve" and overly aggressive [20, 50–52].

Worsening of vision is an important consideration, as it may negatively affect the quality of life of the patients. In large series, the transient postoperative visual impairment was reported in 0.5 to 2.4% with a permanent defect in up to 1.1% [16, 29, 31, 47]. The overall incidence of any postoperative visual worsening in our series was 0.8% and was mainly related to swelling of residual tumor or bleeding into the pituitary fossa. It was permanent in only 0.1% of cases. Postoperative visual deterioration was more frequent in patients with preoperative visual impairment, older than 65 years, and with a giant PA [2, 43, 44]. Oculomotor dysfunction after TSS is reported in the literature up to 2.8% of PAs [31]. In our study, the incidence of transient postoperative oculomotor dysfunction was 0.5%. The defect was evident 24–48 h after surgery and disappeared spontaneously in all patients in the next 2 months.

Water and electrolyte disturbances are usually considered as a minor side effect of TSS, even though both

complications can cause lengthening of hospital stay. Persistent postoperative DI occurred in 0.9% of our patients, whereas delayed hyponatremia was detected in 4.8% of cases. In recent studies, the incidence of delayed hyponatremia is reported in 0.1–7.6% of patients. However, some studies may underestimate the incidence of this complication because of a limited collection of data [2, 23, 25, 36]. The incidence of oro-rhino-sinusal complications in our series is far lower compared the largest endoscopic series confirming microsurgical TSS is a true anatomy-sparing approach [24–30].

Conclusion

At present in the literature there is no scientific evidence supporting other techniques as superior to microsurgery to treat PAs. Based on this study, microsurgical TSS is a safe and effective therapy in experienced hands; furthermore the improvement of pituitary functions after surgery is frequent and should be regarded as a positive effect of surgery beside reversal of hormone hypersecretion in HSPAs.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval The study has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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