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Annales d'Endocrinologie 76 (2015) 220–227

Annales d'Endocrinologie
Annals of Endocrinology

Consensus

Non-functioning pituitary adenoma: When and how to operate? What pathologic criteria for typing?☆

Adénomes hypophysaires non fonctionnels : quand et comment opérer ? Quels critères anatomo-pathologiques retenir ?

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Abstract

After diagnosis of non-functioning pituitary adenoma and impact assessment (pituitary deficiency, visual field disorder), the question of management arises between surgery and surveillance. This part of the Consensus document aims to clarify the principal situations encountered in clinical practice (visual disorder, pituitary deficiency, asymptomatic adenoma, etc.), so as to determine which ones indicate surgery and which ones simple surveillance. Particular contexts are also dealt with (elderly patients, young women hoping for pregnancy, etc). The principal surgical techniques (microscopy, endoscopy, etc.) are also considered. Finally, in case of surgery, the principal pathologic criteria are specified (immunolabeling, proliferation markers, etc.).

Keywords: Pituitary adenoma; Pituitary deficiency; Visual field defect; Elderly subject; Pregnancy; Ki67; p53; Silent pituitary adenoma

Résumé

Après l'étape de diagnostic positif d'adénome hypophysaire non sécrétant, et l'étape d'évaluation du retentissement (déficit hypophysaire, altérations campimétriques), se pose la question de la prise en charge : chirurgie ou surveillance. Cette partie du consensus a pour objectif de déterminer quelles situations rencontrées en pratique clinique (altération campimétrique, déficit hypophysaire, absence de retentissement…) justifient d'une prise en charge chirurgicale ou d'une simple surveillance. Les cas particuliers tels que le sujet âgé, la femme jeune avec désir de grossesse… seront également évoqués. Enfin seront précisés les principales techniques chirurgicales, et les renseignements indispensables que devra comporter le compte-rendu anatomo-pathologique.

Mots clés : Adénome hypophysaire ; Déficit hypophysaire ; Anomalie du champ visuel ; Sujet âgé ; Grossesse ; Ki67 ; p53 ; Adénome hypophysaire silencieux

DOIs of original articles: http://dx.doi.org/10.1016/j.ando.2015.04.004, http://dx.doi.org/10.1016/j.ando.2015.04.006, http://dx.doi.org/10.1016/j.ando.2015.04.002, http://dx.doi.org/10.1016/j.ando.2015.04.005, http://dx.doi.org/10.1016/j.ando.2015.04.003

☆ Consensus of the French Endocrine Society: Non-functioning pituitary adenoma.

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http://dx.doi.org/10.1016/j.ando.2015.04.007
0003-4266/

1. Introduction

After diagnosis of non-functioning pituitary adenoma and impact assessment (pituitary deficiency, visual field disorder), the question of management arises, between surgery and surveillance. This part of the Consensus document aims to clarify the principal situations encountered in clinical practice, and to specify the criteria rendering surgery necessary, possible, or else, debatable with respect to simple surveillance. The principal surgical techniques are specified. Finally, the principle pathologic criteria to be determined on the operative specimen in case of surgery are defined to adapt postoperative treatment in case of remnant.

2. Indications for surgery

2.1. Symptomatic adenoma

2.1.1. Visual disorders

Improved vision is reported in some 80–90% of cases (including both partial and total recovery) [1,2]. Recovery may be progressive, over a period of up to 1 year after surgery. Some studies highlighted a correlation between percentage recovery and duration and severity of campimetric disorder (acuity < 1/10 or optic atrophy being of poor prognosis) [3,4]. In case of demonstrable visual disorder, surgery should therefore not be delayed; the urgency depends on the severity of visual impact. There are no clear data for a threshold time beyond which visual recovery after chiasma decompression is no longer possible. Visual disorders are an indication for surgery, even though complete recovery cannot be guaranteed.

2.1.2. Pituitary deficiency

The risk of onset of further pituitary deficiency associated with macroadenoma is estimated at 12% per year. Arafah et al. correlated preoperative deficiency, headaches and hyperprolactinemia to the potential for postoperative recovery: when all the criteria were met, postoperative recovery of deficiency and improvement in headaches were more frequent [5,6], correlating with intrasellar pressure. Surgery provided recovery of normal anterior pituitary function in about 30% of cases, at a mean of 1-year follow-up [7]; the rate was higher for earlier management. Some teams indeed recommend surgery at the asymptomatic stage of macroadenoma [7]. The risk of postoperative deterioration in pituitary function is about 10% [3]. Postoperative recovery being uncertain, pituitary deficiency is thus probably not the main factor indicating surgery.

2.1.3. Headaches

The involvement of pituitary adenoma in headaches can only be established after ruling out all other possible causes (possibly after referral to a neurologist) and determining time of onset in relation to the natural history of the adenoma.

Headaches are classically due to distension of the dural envelopes [8]. Retro-orbital or vertex locations suggest pituitary etiology. If headaches do indeed implicate adenoma, surgery seems to be effective in relieving symptoms [3,9,10]. Disabling headache implicating adenoma thus seems to be an indication for non-emergency surgery, warning the patient that no direct causal relation can be proven and thus results cannot be guaranteed.

2.2. Asymptomatic adenoma

Surgical indications are founded on several factors:

- patient age. Non-emergency surgery may be considered in young patients without awaiting progression, given the low risk of postoperative visual impairment, the almost inevitable progression of adenoma over the long term, and the risk of definitive postoperative visual impairment if surgery is delayed awaiting onset of a campimetric visual-field effect;
- the natural history of non-functioning adenoma (possible spontaneous increase or decrease in tumor volume). Losa et al. recently stressed that the risk of postoperative recurrence was lower with early surgery [11];
- the risk of onset of campimetric impairment, correlated with the rate of tumor growth and proximity to the optic pathways;
- the risk of onset of pituitary deficiency (12% per year in macroadenoma);
- the risk of apoplexy (estimated at 1% per year in the absence of extra risk factors: see corresponding Consensus article);
- risks inherent to trans-sphenoidal surgery: mortality is less than 1%; the risk of severe adverse events (osteomeningeal breach, meningitis, visual deterioration) is less than 5%; the risk of diabetes insipidus may reach 10%.

Progression is slow in microadenoma and surgery is not indicated. The natural progression of macroadenoma may indicate non-emergency surgery, depending on evolutive status, proximity to the optic pathways, and the patient's age.

2.3. Special cases

2.3.1. Elderly patients

Most studies set a threshold of 65 years for elderliness: physiological age would seem more relevant. There are, however, no data on complications or efficacy in patients aged over 75 years at diagnosis. Most studies combined secreting and non-secreting adenomas, making it difficult to know whether the complications reported relate exclusively to non-secreting adenoma.

Non-functioning adenoma accounts for 60–80% of adenomas in the "elderly", with incidence around 7% [12–14]. Characteristics seem to be identical to those found in "young" subjects, particularly as regards signs at diagnosis: the main presenting symptom is visual impairment, in 50–70% of cases [13]. Most patients present with macroadenoma of 2–4 cm on the long axis [12].

Therapeutic decision-making needs to take account of visual impact, proximity to the chiasm, and comorbidity: 80% of patients have at least 1 comorbidity [12]. Anesthesia risk assessment is crucial, 10% of patients having ASA risk scores contraindicating surgery [15]. One study suggested that non-secreting adenoma growth is slower in elderly subjects [16]. The risk of apoplexy, in the absence of extra risk factors (notably,

antiplatelet and anticoagulant treatments) is identical to that for the pituitary adenoma population as a whole [17].

Mortality is no higher than in the general population if anesthesia risk is well assessed (< 1% of mortality) [13]. The rates of visual recovery and recovery of pituitary deficiency are comparable to that of young subjects: 75% and 30%, respectively. Studies have reported higher rates of mortality and complications associated with craniotomy than with trans-sphenoidal surgery, and the latter approach should be the reference: the risk of severe complications (breach, meningitis) is identical. Hospital stay is longer (up to 20 days, depending on the report) [12], which may be due to a slightly higher rate of postoperative hydro-electrolytic disorder (10% versus 6% in the general population) [14], although some studies fail to confirm it and find no age-related difference [13,15]. There is a risk of visual deterioration in 1–10% of cases.

Indications in 65–75 year-olds are the same as in young subjects, if comorbidity, anesthesia risk and patient impact are well assessed. In case of surgery, the approach should preferably be trans-sphenoidal, so as not to increase the risk of complications. In the absence of visual impact, simple annual MRI surveillance is sufficient. The lack of data for over 75 year-olds is to be borne in mind.

2.3.2. *Young women with or without pituitary deficiency*

Non-functioning adenoma is rare in young women, and published data are sparse [18].

In case of visual field impairment, surgery is mandatory and should be undertaken quickly [19].

In the absence of visual field impairment in a patient with macroadenoma and hoping for pregnancy, the decision to operate may be based on gonadotroph deficiency: surgery provides pituitary recovery in about 30% of cases (depending on progression), while deficiency is found at diagnosis in more than 80% of cases [8]. Gonadotroph deficiency may also be due to disconnection hyperprolactinemia, which usually resolves with surgery [19].

When pregnancy is sought and there is no gonadotroph deficiency, the risk of tumor growth during pregnancy needs to be taken into account, although it is theoretically low, pregnancy being principally characterized by lactotroph cell hyperplasia; however, in association with macroadenoma, this may cause chiasmal compression, as reported in some cases [18,20]. The decision to operate should therefore be based on adenoma size and proximity to the optic pathways: maximum pituitary gland height can increase by 12 mm during pregnancy [19]. In abstention from surgery, clinical surveillance should be at least 3-monthly, with visual field test and MRI without contrast enhancement in case of tumoral syndrome onset during pregnancy. The risk of apoplexy is slightly increased during pregnancy [17].

If there is no pregnancy project in the medium term and no pituitary deficiency, the decision to operate is guided by the natural history of non-functioning adenoma: specifically, size and proximity to the optic pathways. Surgery is not urgent. It is not indicated in microadenoma, and may be considered on a non-emergency basis in macroadenoma remote from the optic pathways. Dekkers et al. reported that the risk of increase in macroadenoma size probably correlated with length of follow-up, with increase in 50% of cases for ≥ 5-years follow-up. Spontaneous reduction in size is rarer, reported in 11% of cases [3]. Two attitudes are possible: MRI surveillance with surgery in case of progression, or first-line surgery [21]. Progression from micro- to macro-adenoma is rare; in microadenoma in a young female patient, emergency surgery is therefore not indicated except in case of progression on MRI at 6 months to 1 year [3].

For young female patients, surgery should respond quickly to any impairment of visual field. Gonadotroph deficiency is also an indication for surgery, although postoperative recovery is unsure. Pregnancy is not theoretically a risk factor for increasing adenoma volume, but there is a risk of campimetric impairment if the adenoma is close to the optic pathways. In that case, surgery should be considered; if it is not implemented, close clinical surveillance and visual field testing should accompany the pregnancy. If no pregnancy is planned and the adenoma shows no impact, MRI surveillance should be proposed, or else surgical intervention without awaiting progression.

2.3.3. *Antiplatelets and anticoagulants*

Anticoagulants: in the general population, the incidence of hemorrhage associated with anti-vitamin K (AVK) is estimated at 7% per year, and mortality at 1% [22]. AVK is associated with 7 to 10-fold elevation of spontaneous intracerebral bleeding. Withdrawal of AVK (in favor of heparin) is recommended 5 days ahead of surgery, to obtain normal INR (international normalized ratio), with reintroduction in the following 7 to 14 days.

Antiplatelets: the risk of intracranial hemorrhage is low. A study of meningioma surgery, however, associated antiplatelets with postoperative hematoma [23]. Preoperative withdrawal, on the other hand, is associated with increased morbidity and mortality, especially in patients with active stents; withdrawal thus requires the opinion of a cardiologist, 5 days ahead of surgery for aspirin and ideally 10 days ahead of surgery for clopidogrel.

Published data are scarce. A French study of 546 patients undergoing adenoma surgery while under long-course anticoagulants or antiplatelets reported a 6-folds rise in risk of postoperative hemorrhagic complications (epistaxis or hematoma of the operative cavity in 6% of cases, compared to 0.9% in the group without anticoagulants or antiplatelets) [24].

There are presently no guidelines on withdrawal of anticoagulants and antiplatelets. Continuation doubtless increases the risk of postoperative hematoma. The decision should be made in coordination with the neurosurgeon, cardiologist and anesthesiologist.

Long-course anticoagulants or antiplatelets also increase the risk of pituitary apoplexy, which should be taken into account in deciding between surveillance and surgery.

3. Surgical options

Surgery for pituitary adenoma is no exception to the modernization of techniques and operating theater environment: diagnostic MRI, endoscopy, neuronavigation, intra-operative

imaging. It is to be borne in mind that non-functioning adenoma is rarely aggressive, and a systematically maximalist attitude is to be eschewed. In certain cases, however, 2-step or extended surgery, possibly using an endocranial approach, may be necessary due to the complexity and/or aggressiveness of the tumor.

3.1. Endoscopy versus microsurgery

In non-functioning pituitary adenoma, which is almost always macroadenoma, surgery aims at optimal resection with minimal morbidity. Complete resection is certainly desirable, preventing recurrence or progression. At each stage of management, potential iatrogenic morbidity is to be weighed against the frequently benign nature of these tumors, and this balance is to be struck on a case-by-case basis. The quality of present-day imaging enables very reliable long-term follow-up, which may allow partial or subtotal resection, at lower cost, rather than complete resection with its risk of complications.

Since the 1960s and the work of Guiot and Hardy, the gold standard for pituitary surgery has involved a trans-sphenoidal approach under operative microscopy and intra-operative radiological guidance [25,26]. The approach was initially described as sublabial rhinoseptal trans-sphenoidal: i.e., under the upper lip, along the nasal septum and across the sphenoidal septum. The surgeon made an incision in the superior gingival groove, resected or dislocated the nasal septum, removed the sphenoidal rostrum and opened the sphenoidal sinus to insert a speculum. Access to the adenoma was via the sella turcica floor, by fragmentation-aspiration resection. To simplify nasal postoperative course and increase comfort, a pure endonasal approach was introduced by Griffith and Veerapenen in 1987 [27]. In this variant of the sublabial approach, the surgeon accessed the sphenoidal sinus directly via one of the nasal cavities. Once the speculum was in position and the sphenoidal sinus open, surgery proceeded as on a sublabial approach. A recent modification by Kerr and Oldfield in 2008 did not greatly differ from the reference technique developed by Guiot and Hardy [28]. Since then, no randomized studies have demonstrated superiority between the initial technique and any of its variants, or indeed superiority for microscopy, although it is incontestably essential in neurosurgery and pituitary pathology.

Techniques, however, have shifted in favor of endoscopy, due to the frequent problem of postoperative residua (ranging from 70% to 10% in the main series) and the discomfort of several days' nasal packing and frequent upper gum hypoesthesia, combined with progress in nasal endoscopy in ENT pathology.

In the early 1990s, following an initial publication by Jankowski et al. in 1992 and North American and Italian studies, endoscopy began to compete with microscopy, which it replaced in certain teams [29–32]. Postoperative comfort is better. Complication rates, once the initial learning curve has passed, are comparable between microsurgery and endoscopy [33–36]. There have been no prospective randomized series to demonstrate superiority one way or the other, but the experience of expert pituitary surgery teams testifies to better control of lateral and superior extension under endoscopy and a review of endoscopically managed non-functioning pituitary adenomas found a higher mean rate of macroscopically total resection [34,37]. Catapano et al.'s cadaver studies and Mattozzo et al.'s clinical studies of patients undergoing surgical revision for residuum found wider sella turcica opening with endoscopy compared to microscopy and, in the latter study, that primary opening had been too narrow [38,39]. Finally, a recent meta-analysis by Ammirati et al. found no benefit of endoscopy over microscopy in terms of resection quality, but rather a higher rate of vascular complications; the meta-analysis, however, covered all endoscopy series, including early learning curves, whereas the microscopy series reported results from teams beyond the learning stage [40].

At all events, microscopy surgery is progressively being replaced by endoscopy; more than the instrument, however, it is the surgeon's experience that counts. Objectives and indications are the same, in either case. Placing endonasal pituitary surgery in the context of other surgical specialties (urology, ENT, abdominal and gynecological laparoscopic surgery) treating hollow organs or using cavities such as the nasal fossae, it is more than likely that, within two decades from now, endoscopy will have entirely supplanted microscopy in pituitary adenoma surgery.

Complications are few in pituitary surgery (essentially, ENT, endocrine or ophthalmologic morbidity, osteomeningeal breach, meningitis and vascular wounds) and directly correlated with the surgeon's experience, arguing for hyperspecialization in pituitary neurosurgery [41,42].

3.2. Two-step surgery, extended and endocranial approaches

Endoscopy also enables extended approaches, with access to the intradural compartment, by removing the tuberculum sellae, chiasmatic groove and posterior part of the jugum sphenoidale (transtubercular approach). This may be useful in case of suprasellar extension that refuses to descend after intrasellar debulking. In this case, 2-step surgery may also be considered: cerebral pulsation will, in many cases, cause the suprasellar expansion to migrate into the sella turcica, rendering it accessible on a repeated classical trans-sphenoidal approach. Two-step surgery is less aggressive than an extended approach, although requiring a second general anesthesia and second hospital admission. The intra-operative decision criteria are subjective. Two-step surgery is a useful option if the suprasellar residuum is not too large and intra-operative hemostasis can be achieved. Otherwise, there is a severe risk of hemorrhagic apoplexy of the suprasellar fragment, and an extended 1-step procedure is preferable. The decision is made intra-operatively. Situations encountered can be very variable; attitudes vary from team to team, and it is difficult to draw up any rule. Likewise for endocranial approaches: in some rare cases of sometimes giant adenoma with anterior, retroclival or lateral extension toward the Sylvian fissure, or "mushrooming" in or toward the central gray nuclei, either an isolated endocranial approach or a combined endocranial and transsphenoidal approach, in a single step or at a few days' or weeks' interval, may be used [43–45]. There are no rules as to the sequence and timing of a combined approach.

Indications are rare and mainly concern expert centers; the decision depends essentially on tumor extension, but also on team experience and habits.

3.3. Role and benefit of intra-operative imaging

Historically, the first method of intra-operative guidance was radioscopy, providing information exclusively in the sagittal plane. The method is now obsolete, and moreover exposes all those present in the surgery room, as well as the patient, to ionizing radiation.

Neuronavigation based on preoperative CT and/or MRI provides information in all 3 planes and is the method now used for intra-operative guidance in neurosurgery. Resolution is now of the order of a millimeter [46]. There are no randomized studies demonstrating benefit, but it is applicable in the following circumstances:

- training: notably in the early learning curve, to gain familiarity with the endonasal endoscopic approach;
- teaching: to point out the anatomic details of the various stages of the approach;
- in case of unusual anatomy or remodeling (sinus concha, acromegaly);
- when the usual anatomic landmarks are liable to be lost, as in adenoma that has destroyed or invaded the sphenoidal sinus, or in surgery for recurrence in which the previous landmarks have been damaged or removed by primary surgery;
- whenever surgery is "extended" to structures neighboring the sella turcica.

Intra-operative CT and/or MRI are probably the attitude of the future. In a non-dedicated surgery room, however, only a low-field low-definition system is feasible. High fields (1.5 Tesla and above) are more reliable in assessing intra-operative residua, but require specific and very costly equipment, not available in most centers. The true benefit of intra-operative MRI remains to be established [47]. Publications from centers in which it is used have been encouraging [48–51].

4. Anatomopathology

4.1. General considerations

Clinically and/or biologically non-functioning pituitary adenoma cover 3 different histologic types according to the current pathology classifications [52]:

- gonadotroph adenoma (FSH/LH) and the non-immunoreactive variant known as "null cell adenoma", which constitute the great majority [53–55];
- silent corticotroph adenoma (ACTH), also known as "silent type 1 or 2 adenoma" (reviewed in [56]);
- and silent somatotroph (GH) or mixed GH-PRL adenoma (GH-PRL ± TSH), also known as "silent subtype 3" [57–59].

The first clinical [60] and histological [61] descriptions of pituitary adenoma with FSH hypersecretion date back to almost 40 years, and the first series (8 cases) of gonadotroph adenoma with and without LH/FSH hypersecretion to more than 30 years [55].

In Lyon (France), pathology series of more than 3000 tumors studied immunocytochemically since 1986, the rate of non-functioning adenoma was 35%. With improvements in the sensitivity and reproducibility of automated immunocytochemistry since 2007, the proportion of non-immunoreactive adenomas has fallen from 15% to 1% and that of gonadotroph adenoma has risen from 22% to 35% (178/502 tumors operated on in 2007–2012). Silent GH-PRL and ACTH adenoma now accounts for 8% of operated adenomas and 18% of non-functioning adenomas (40/218), silent ACTH adenoma being the most frequent form. In clinical and neurosurgical series, these 3 types of non-functioning adenoma are often, mistakenly, grouped together for analysis, whereas they are in fact very different histologically and clinically, and probably in terms of progression.

4.2. Clinicopathologic data

4.2.1. Tumor size and invasion

At the present time, pathologic diagnosis of pituitary adenoma and of non-functioning adenoma in particular (cf. check-list below) should include imaging data and intra-operative findings to assess tumor size and invasive/non-invasive status, as histological proof is possible in only 10% of tumors found to be invasive on MRI: the intracavernous fragment close to the internal carotid artery is rarely included in the specimen.

4.2.2. Histology, immunocytochemistry and proliferation

Non-functioning adenoma is identifiable on immunohistochemistry, but silent ACTH or GH-PRL adenoma may also be suspected on histology as their aspect resembles their symptomatic clinical variant with acromegaly or Cushing's disease. We deal here only with gonadotroph adenoma.

Gonadotroph adenoma shows diffuse or, more often, a cord arrangement, with well-developed vascularization; in rare cases, it may be hemorrhagic or necrotic. The cells are well-delineated, oval or polyhedral, without signs of secretion (small nuclei without nucleoli). Immunocytochemistry is indispensable, but involves technical problems relating to fixation and antibody specificity. Gonadotroph hormone detection is negative with AFA fixation and rare with 4% buffered formaldehyde; some antibodies show negative or non-specific reaction. The fixative, preferably formaldehyde-zinc, and the antibody reference (clone) should be specified in the pathology report. In immunocytochemistry, all cells are strongly positive to anti-chromogranin A antibodies. Thus, strongly and diffusely expressed chromogranin A in necrotic adenoma suggests gonadotroph adenoma, reaction with anti-pituitary hormone antibodies being usually negative. In gonadotroph adenoma, the percentage of cells immunoreactive to anti-gonadotroph hormone antibodies varies from 100% to a few islands, and is usually low (20–30%), with immunoreactive cells localized by

area (Appendix A). In some tumors, cells are positive for all 3 βFSH, βLH and α-sub-unit antibodies, while in others they are positive only for βFSH or, more rarely, βLH or α sub-unit. When only few cells (< 5%) are immunoreactive, null-cell type adenoma is diagnosed, although it secretes gonadotroph hormones in culture and shows granulation on electron microscopy. Plurihormonal gonadotroph adenoma is rare, except in type-1 multiple endocrine neoplasia (MEN1) [62]. In case of remnant and especially of progression, somatostatin receptor detection is performed, using new highly specific antibodies to guide somatostatin analog prescription: 26% of gonadotroph adenomas express type-2 somatostatin receptor (SSTR2), SSTR5 being rare and often focal [63].

To assess the risk of recurrence or progression, it is important to specify proliferative status by systematically testing the 3 proliferation markers: proliferation index assessed on Ki-67 antibody, mitotic activity, and p53 expression. Ki-67 expression has been especially well studied [64,65]. Results concerning association with invasiveness and recurrence/progression are contradictory. However, automated immunocytochemistry makes detection of these nuclear markers more reproducible, and analysis of the literature, including the recent studies by Jaffrain-Rea et al., [66] and Righi et al., [67], shows that Ki-67 > 3% predicts recurrence/progression with high specificity (89%) but poor sensitivity (54%). The interest of mitotic activity and p53 expression is even more debatable. We suggest noting, in the pathology report, the number of mitoses per 10 wide fields with a 40× magnification lens, with a threshold of $n > 2$, and P53 expression (positive for > 10 positive nuclei per 10 wide fields at 40×), or as percentages. In some recurrent tumors or even carcinomas with metastasis, the Ki-67 index may be low and the mitosis count high. We therefore recommend testing all 3 markers systematically, classifying the tumor as proliferative only when at least 2 are above threshold. Following the multidisciplinary multicenter HYPOPRONOS study, we recommend a new classification in 5 grades, the prognostic value of which has been demonstrated on multivariate analysis ($P < 0.001$) [68]. Other molecular markers have also been described for non-functioning pituitary adenoma, but their prognostic value with regard to recurrence and progression remains to be validated.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Appendix A. Pathology check-list

I. MRI

	Size:	Micro	Macro	Giant
	Invasion:	yes	no	
If yes:				
	Cavernous sinus		yes	no
	Sphenoidal sinus		yes	no
	Intra-operative confirmation		yes	no

II. Histology

1. Fixatives

Formaldehyde-zinc	yes	no
Bouin Hollande	yes	no

NB: Other fixatives (AFA, neutral formaldehyde) not recommended due to ICC problems.

2. Histology

	Invasion	yes	no	ND
If yes:	Location			
Cavernous sinus	Sphenoidal sinus	Dura-mater	Juxta-tumoral pituitary gland	

3. ICC

a) Antibodies for typing
- ßFSH, ßLH, αSU, Chromogranin A → gonadotroph adenoma
- PRL–GH → silent GH or GH/PRL adenoma
- ACTH → silent corticotroph adenoma

b) For proliferation

Mitosis count n =	(threshold, $n > 2$/10 40× fields)
Ki-67 index:	(threshold ≥ 3%)
P53 detection:	(+ for > 10 nuclei/10 40× fields)

To be discussed: type 2 and 5 somatostatin receptors

III. Molecular biology

To be discussed: fragment freezing and conservation at –80 °C for micro-array, PCR and CGH study.

References

[1] Dehdashti AR, Ganna A, Karabatsou K, Gentili F. Pure endoscopic endonasal approach for pituitary adenomas: early surgical results in 200 patients and comparison with previous microsurgical series. Neurosurgery 2008;62:1006–15 [Discussion 1015–7].

[2] Tabaee A, et al. Predictors of short-term outcomes following endoscopic pituitary surgery. Clin Neurol Neurosurg 2009;111:119–22.

[3] Dekkers OM, Pereira AM, Romijn JA. Treatment and follow-up of clinically nonfunctioning pituitary macroadenomas. J Clin Endocrinol Metab 2008;93:3717–26.

[4] Gnanalingham KK, Bhattacharjee S, Pennington R, Ng J, Mendoza N. The time course of visual field recovery following transphenoidal surgery for pituitary adenomas: predictive factors for a good outcome. J Neurol Neurosurg Psychiatry 2005;76:415–9.

[5] Arafah BM, Kailani SH, Nekl KE, Gold RS, Selman WR. Immediate recovery of pituitary function after transsphenoidal resection of pituitary macroadenomas. J Clin Endocrinol Metab 1994;79:348–54.

[6] Arafah BM, Prunty D, Ybarra J, Hlavin ML, Selman WR. The dominant role of increased intrasellar pressure in the pathogenesis of hypopituitarism, hyperprolactinemia, and headaches in patients with pituitary adenomas. J Clin Endocrinol Metab 2000;85:1789–93.

[7] Messerer M, et al. Non-functioning pituitary macro-incidentalomas benefit from early surgery before becoming symptomatic. Clin Neurol Neurosurg 2013;115:2514–20.

[8] Murad MH, et al. Outcomes of surgical treatment for nonfunctioning pituitary adenomas: a systematic review and meta-analysis. Clin Endocrinol (Oxf) 2010;73:777–91.

[9] Comtois R, et al. The clinical and endocrine outcome to trans-sphenoidal microsurgery of nonsecreting pituitary adenomas. Cancer 1991;68:860–6.

[10] Wichers-Rother M, Hoven S, Kristof RA, Bliesener N, Stoffel-Wagner B. Non-functioning pituitary adenomas: endocrinological and clinical

outcome after transsphenoidal and transcranial surgery. Exp Clin Endocrinol Diabetes 2004;112:323–7.
[11] Losa M, Donofrio CA, Barzaghi R, Mortini P. Presentation and surgical results of incidentally discovered nonfunctioning pituitary adenomas: evidence for a better outcome independently of other patients' characteristics. Eur J Endocrinol 2013;169:735–42.
[12] Hong J, Ding X, Lu Y. Clinical analysis of 103 elderly patients with pituitary adenomas: transsphenoidal surgery and follow-up. J Clin Neurosci 2008;15:1091–5.
[13] Minniti G, et al. Diagnosis and management of pituitary tumours in the elderly: a review based on personal experience and evidence of literature. Eur J Endocrinol 2005;153:723–35.
[14] Turner HE, Adams CB, Wass JA. Pituitary tumours in the elderly: a 20 year experience. Eur J Endocrinol 1999;140:383–9.
[15] Locatelli M, Bertani G, Carrabba G, et al. The trans-sphenoidal resection of pituitary adenomas in elderly patients and surgical risk. Pituitary 2013;16:146–51.
[16] Losa M, et al. Proliferation index of nonfunctioning pituitary adenomas: correlations with clinical characteristics and long-term follow-up results. Neurosurgery 2000;47:1313–8 [Discussion 1318–9].
[17] Liu ZH, et al. Predisposing factors of pituitary hemorrhage. Eur J Neurol 2012;19:733–8.
[18] Kupersmith MJ, Rosenberg C, Kleinberg D. Visual loss in pregnant women with pituitary adenomas. Ann Intern Med 1994;121:473–7.
[19] Molitch ME. Pituitary tumors and pregnancy. Growth Horm IGF Res 2003;13(Suppl A):S38–44.
[20] Masding MG, Lees PD, Gawne-Cain ML, Sandeman DD. Visual field compression by a non-secreting pituitary tumour during pregnancy. J R Soc Med 2003;96:27–8.
[21] Fernandez-Balsells MM, et al. Natural history of nonfunctioning pituitary adenomas and incidentalomas: a systematic review and metaanalysis. J Clin Endocrinol Metab 2011;96:905–12.
[22] Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. Ann Intern Med 2003;139:893–900.
[23] Palmer JD, Sparrow OC, Iannotti F. Postoperative hematoma: a 5-year survey and identification of avoidable risk factors. Neurosurgery 1994;35:1061–4 [Discussion 1064–5].
[24] Aldea S, Tremey B, Dupuy M, Gaillard S. Anticoagulant and antiplatelet therapy in pituitary gland and skull base surgery. Neurochirurgie 2009;55:H36–9.
[25] Guiot G, Bouche J, Oproiu A. [Indications of the trans-sphenoidal approach to pituitary adenomas. Experience with 165 operations]. Presse Med 1967;75:1563–8.
[26] Hardy J, Wigser SM. Trans-sphenoidal surgery of pituitary fossa tumors with televised radiofluoroscopic control. J Neurosurg 1965;23:612–9.
[27] Griffith HB, Veerapen R. A direct transnasal approach to the sphenoid sinus. Technical note. J Neurosurg 1987;66:140–2.
[28] Kerr PB, Oldfield EH. Sublabial-endonasal approach to the sella turcica. J Neurosurg 2008;109:153–5.
[29] Cappabianca P, Alfieri A, de Divitiis E. Endoscopic endonasal transsphenoidal approach to the sella: towards functional endoscopic pituitary surgery (FEPS). Minim Invasive Neurosurg 1998;41:66–73.
[30] Carrau RL, Jho HD, Ko Y. Transnasal-transsphenoidal endoscopic surgery of the pituitary gland. Laryngoscope 1996;106:914–8.
[31] Jankowski R, et al. Endoscopic pituitary tumor surgery. Laryngoscope 1992;102:198–202.
[32] Jho HD, Carrau RL, Ko Y, Daly MA. Endoscopic pituitary surgery: an early experience. Surg Neurol 1997;47:213–22 [Discussion 222–3].
[33] Cappabianca P, Cavallo LM, Colao A, de Divitiis E. Surgical complications associated with the endoscopic endonasal transsphenoidal approach for pituitary adenomas. J Neurosurg 2002;97:293–8.
[34] Messerer M, et al. Evidence of improved surgical outcome following endoscopy for nonfunctioning pituitary adenoma removal. Neurosurg Focus 2011;30:E11.
[35] Gondim JA, et al. Endoscopic endonasal approach for pituitary adenoma: surgical complications in 301 patients. Pituitary 2011;14:174–83.
[36] Duntze J, et al. [Cerebrospinal fluid rhinorrhea following endocopic trans-sphenoidal pituitary surgery: experience from 337 patients]. Neurochirurgie 2012;58:241–5.
[37] Rotenberg B, Tam S, Ryu WH, Duggal N. Microscopic versus endoscopic pituitary surgery: a systematic review. Laryngoscope 2010;120:1292–7.
[38] Catapano D, et al. Comparison between the microscope and endoscope in the direct endonasal extended transsphenoidal approach: anatomical study. J Neurosurg 2006;104:419–25.
[39] Mattozo CA, et al. Suboptimal sphenoid and sellar exposure: a consistent finding in patients treated with repeat transsphenoidal surgery for residual endocrine-inactive macroadenomas. Neurosurgery 2006;58:857–65 [Discussion 857–65].
[40] Ammirati M, Wei L, Ciric I. Short-term outcome of endoscopic versus microscopic pituitary adenoma surgery: a systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 2013;84:843–9.
[41] Barker FG, 2nd, Klibanski A, Swearingen B. Transsphenoidal surgery for pituitary tumors in the United States, 1996-2000: mortality, morbidity, and the effects of hospital and surgeon volume. J Clin Endocrinol Metab 2003;88:4709–19.
[42] Ciric I, Ragin A, Baumgartner C, Pierce D. Complications of transsphenoidal surgery: results of a national survey, review of the literature, and personal experience. Neurosurgery 1997;40:225–36 [Discussion 236–7].
[43] Nishioka H, Hara T, Usui M, Fukuhara N, Yamada S. Simultaneous combined supra-infrasellar approach for giant/large multilobulated pituitary adenomas. World Neurosurg 2012;77:533–9.
[44] Zada G, Du R, Laws Jr ER. Defining the "edge of the envelope": patient selection in treating complex sellar-based neoplasms via transsphenoidal versus open craniotomy. J Neurosurg 2011;114:286–300.
[45] Zada G, Laws Jr ER. Simultaneous transsphenoidal and intraventricular endoscopic approaches for macroadenomas with extensive suprasellar extension: surgery from below, above, or both? World Neurosurg 2010;74:109–10.
[46] Zhao Y, Yu S, Wang R, Zhao J. Clinical application of a neuronavigation system in transsphenoidal surgery of pituitary macroadenoma. Neurosurg Rev 2006;29:306–11 [Discussion 311–2].
[47] Eboli P, Shafa B, Mayberg M. Intraoperative computed tomography registration and electromagnetic neuronavigation for transsphenoidal pituitary surgery: accuracy and time effectiveness. J Neurosurg 2011;114:329–35.
[48] Bellut D, Hlavica M, Schmid C, Bernays RL. Intraoperative magnetic resonance imaging-assisted transsphenoidal pituitary surgery in patients with acromegaly. Neurosurg Focus 2010;29:E9.
[49] Berkmann S, Fandino J, Muller B, Remonda L, Landolt H. Intraoperative MRI and endocrinological outcome of transsphenoidal surgery for non-functioning pituitary adenoma Acta Neurochir (Wien) 2012;154:639–47.
[50] Berkmann S, et al. Intraoperative magnetic resonance imaging and early prognosis for vision after transsphenoidal surgery for sellar lesions. J Neurosurg 2011;115:518–27.
[51] Ramm-Pettersen J, et al. Intra-operative MRI facilitates tumour resection during trans-sphenoidal surgery for pituitary adenomas. Acta Neurochir (Wien) 2011;153:1367–73.
[52] DeLellis R, Lloyd R, Heitz P, Eng C. World Health Organization classification of tumours: pathology and genetics of tumours of endocrine organs. Ed. Press, L.I.; 2004.
[53] Trouillas J, et al. [Normal and tumorous human gonadotropic cells]. Ann Endocrinol (Paris) 1990;51:54–64.
[54] Trouillas J, Girod C, Sassolas G, Claustrat B. The human gonadotropic adenoma: pathologic diagnosis and hormonal correlations in 26 tumors. Semin Diagn Pathol 1986;3:42–57.
[55] Trouillas J, et al. Human pituitary gonadotropic adenoma; histological, immunocytochemical, and ultrastructural and hormonal studies in eight cases. J Pathol 1981;135:315–36.
[56] Raverot G, et al. Clinical, hormonal and molecular characterization of pituitary ACTH adenomas without (silent corticotroph adenomas) and with Cushing's disease. Eur J Endocrinol 2010;163:35–43.
[57] Trouillas J, et al. Somatotropic adenomas without acromegaly. Pathol Res Pract 1991;187:943–9.

[58] Erickson D, et al. Silent subtype 3 pituitary adenoma: a clinicopathologic analysis of the Mayo Clinic experience. Clin Endocrinol (Oxf) 2009;71:92–9.
[59] Kovacs K, et al. Silent somatotroph adenomas of the human pituitary. A morphologic study of three cases including immunocytochemistry, electron microscopy, in vitro examination, and in situ hybridization. Am J Pathol 1989;134:345–53.
[60] Snyder PJ, Sterling FH. Hypersecretion of LH and FSH by a pituitary adenoma. J Clin Endocrinol Metab 1976;42:544–50.
[61] Kovacs K, et al. Pituitary adenomas associated with elevated blood follicle-stimulating hormone levels: a histologic, immunocytologic, and electron microscopic study of two cases. Fertil Steril 1978;29:622–8.
[62] Trouillas J, et al. Pituitary tumors and hyperplasia in multiple endocrine neoplasia type 1 syndrome (MEN1): a case-control study in a series of 77 patients versus 2509 non-MEN1 patients. Am J Surg Pathol 2008;32:534–43.
[63] Chinezu L, et al. Expression of somatostatin receptors, SSTR2A and SSTR5, in 108 endocrine pituitary tumors using immunohistochemical detection with new specific monoclonal antibodies. Hum Pathol 2014;45:71–7.
[64] Dubois S, et al. Relevance of Ki-67 and prognostic factors for recurrence/progression of gonadotropic adenomas after first surgery. Eur J Endocrinol 2007;157:141–7.
[65] Ramirez C, et al. Expression of Ki-67, PTTG1, FGFR4, and SSTR 2, 3, and 5 in nonfunctioning pituitary adenomas: a high throughput TMA, immunohistochemical study. J Clin Endocrinol Metab 2012;97:1745–51.
[66] Jaffrain-Rea ML, et al. A critical reappraisal of MIB-1 labelling index significance in a large series of pituitary tumours: secreting versus non-secreting adenomas. Endocr Relat Cancer 2002;9:103–13.
[67] Righi A, et al. A classification tree approach for pituitary adenomas. Hum Pathol 2012;43:1627–37.
[68] Trouillas J, et al. A new prognostic clinicopathological classification of pituitary adenomas: a multicentric case-control study of 410 patients with 8 years post-operative follow-up. Acta Neuropathol 2013;126:123–35.