



HAL
open science

Clinically non-functioning pituitary adenomas

Philippe Chanson, Peter Wolf

► **To cite this version:**

Philippe Chanson, Peter Wolf. Clinically non-functioning pituitary adenomas. La Presse Médicale, 2021, 50 (4), pp.104086. 10.1016/j.lpm.2021.104086 . hal-04323510

HAL Id: hal-04323510

<https://universite-paris-saclay.hal.science/hal-04323510>

Submitted on 22 Jul 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

CLINICALLY NON-FUNCTIONING PITUITARY ADENOMAS

Philippe Chanson¹, Peter Wolf^{1,2}

1 Université Paris-Saclay, Inserm, Physiologie et Physiopathologie Endocriniennes, Assistance Publique-Hôpitaux de Paris, Hôpital Bicêtre, Service d'Endocrinologie et des Maladies de la Reproduction, Centre de Référence des Maladies Rares de l'Hypophyse, 94275 Le Kremlin-Bicêtre, France;

2 Medical University of Vienna, Department of Internal Medicine III, Division of Endocrinology and Metabolism, 1090 Vienna, Austria;

Corresponding author:

Philippe Chanson, Service d'Endocrinologie et des Maladies de la Reproduction, Hôpitaux Universitaires Paris-Sud, Site Bicêtre, 94275 Le Kremlin-Bicêtre Cedex, France.

Tel.: 33 1 45 21 37 08

Fax: 33 1 45 21 22 12

e-mail: philippe.chanson@aphp.fr

Word count: 4879

Conflicts of interest disclosure

The authors declare that they have no competing interest.

CLINICALLY NON-FUNCTIONING PITUITARY ADENOMAS

Word count: 4879

Conflicts of interest disclosure

The authors declare that they have no competing interest.

Abstract

Clinically non functioning pituitary adenomas (NFPAs) include all pituitary adenomas that are not hormonally active. They are not associated with clinical syndromes such as amenorrhea-galactorrhea (prolactinomas), acromegaly, Cushing's disease or hyperthyroidism (TSH-secreting adenomas) and are therefore usually diagnosed by signs and symptoms related to a mass effect (headache, visual impairment, sometimes pituitary apoplexy), but also incidentally. Biochemical work up often documents several pituitary insufficiencies. In histopathology, the majority of NFPAs is gonadotroph. In the absence of an established medical therapy, surgery is the mainstay of treatment, unless contraindicated or in particular situations (e.g. small incidentalomas, distance from optic pathways). Resection, generally *via* a trans-sphenoidal approach (with the help of an endoscope), should be performed by a neurosurgeon with extensive experience in pituitary surgery, in order to maximize the chances of complete resection and to minimize complications. If a tumor remnant persists, watchful waiting is preferred to routine radiotherapy, as long as the tumor residue does not grow and is at distance to the optic pathways. NFPA can sometimes recur even after complete resection, but predicting the individual risk of tumor remnant progression is difficult. Postoperative irradiation is only considered in case of residual tumor growth or relapse, due to its potential side effects.

Keywords

Non functioning pituitary adenomas, pituitary incidentalomas, neurosurgery, radiotherapy, gonadotroph adenomas, mass effect.

“Clinically non functioning pituitary adenomas” (NFPAs) include all pituitary adenomas that are not hormonally active and therefore not result in clinical syndromes such as amenorrhea-galactorrhea (prolactinomas), acromegaly, Cushing’s disease or hyperthyroidism (TSH-secreting adenomas). However, most such NFPAs, which are “chromophobic” on classical histology, in fact secrete gonadotropins or are actually gonadotroph pituitary adenomas. Immunolabeling is negative in only 10% of cases (“null-cell adenomas”). Occasionally, NFPAs are positive for GH, PRL, TSH or ACTH despite absent or only minimal secretion of these hormones *in vivo*, which are known as silent somatotroph, lactotroph, thyrotroph or corticotroph adenomas.

PATHOLOGY

The first patient with a NFPA and increased serum levels of gonadotropins has been reported in 1976, introducing the concept of gonadotroph adenoma (1). Two years later, Kovacs et al. described the histological and immunocytochemical features of FSH-secreting adenomas (2), and this was rapidly followed by publications of series of patients (3, 4). Progressively, with the use of specific monoclonal antibodies applied to the excised lesion, it has become clear, that in the vast majority of cases, these NFPAs (which are “chromophobic” with classical staining techniques), in fact, produce gonadotropins and/or their subunits (β FSH, β LH, α SU) and can thus be considered gonadotroph. This has been confirmed by gene expression studies (5, 6) Gonadotroph adenomas show a diffuse or, more often, cord arrangement, with extensive vascularization. In rare cases they may be hemorrhagic or necrotic. The cells are well-delineated, oval or polyhedral, generally without signs of secretion (small nuclei without nucleoli) (4, 7-9). All cells are strongly positive with anti-

chromogranin A antibodies. The percentage of cells positive with anti-gonadotropin antibodies ranges from 100% to a few islands, but it is usually low (<20–30%). Some tumors contain cells positive for β FSH, β LH and alpha subunit, while others contain cells that are only positive for β FSH or, more rarely, β LH or α SU (4, 10, 11). When less than 5% of the adenomatous cells immunostain positively, the tumor is considered as « null cell adenoma ». Thanks to improved knowledge of pituitary cell differentiation and the availability of cytogenetic markers, the use of several transcription factors including the steroidogenic factor 1 (SF-1), which regulates gonadotroph lineage, allows to classify adenomas independently of hormone expression (7, 9, 12-15).

It remains largely unknown why the gonadotropins in gonadotroph adenomas are seldomly secreted in the bloodstream and, when they are, why they are exceptionally responsible for clinical syndromes related to gonadotropins excess (16-21) but, much more likely, are associated with hypogonadism. Chromatofocusing analysis showed that gonadotroph adenomas produce more basic FSH isoforms (22) which, paradoxically, are considered as more biologically active (23, 24). However, as glycosylation of gonadotropins is essential for their biological activity, hypogonadism might be explained by decreased biological activity of gonadotropins related to abnormal glycosylation of the isoforms produced by the adenoma.

When hormone markers are negative and no pituitary transcription factors are expressed, NFPA is defined as null cell adenoma. Furthermore, NFPAs may also be silent variants of lactotroph, somatotroph or corticotroph adenomas (25). They can be suspected on histology as their aspect resembles that of their symptomatic clinical variant responsible for acromegaly or Cushing's disease. Immunocytochemistry and

the expression of transcription factors allow to make the diagnosis (26). Silent corticotroph adenoma are also called “silent type 1 or 2 adenoma” (27). Positivity for Tpit, which determines corticotroph cell differentiation, is helpful for confirming the corticotroph nature of the adenoma (14). Silent somatotroph or mixed mammo-somatotroph adenoma (GH-PRL ± TSH) are known as “silent subtype 3” (28-30). □ Staining of silent adenomas for the transcription factor Pit-1, which determines somato-lacto-thyrotroph lineage may help to classify these adenomas (14, 31).

Plurihormonal gonadotroph adenomas are rare, except in multiple endocrine neoplasia type-1 (MEN1) (32-34).

Markers of proliferation

Three proliferation markers must be used to assess the risk of recurrence or progression, namely the proliferation index (anti-Ki-67 antibody staining), mitotic activity, and p53 expression. A mitotic count of more than 2 mitoses per 10 HPFs, a Ki-67 expression of more than >3% and more than 10 per HPF strongly positive nuclei for p53 of cells predict tumor recurrence or tumor remnant progression (35-39).

EPIDEMIOLOGY

The prevalence of pituitary adenomas is 80-100 per 100 000 inhabitants, and 15-30% of these adenomas are “non functioning” (40-42). The annual incidence of NFPA is between 10 and 20 cases per million inhabitants (40, 43).

NFPAs are generally diagnosed during the 5th or 6th decade and show a male predominance (16, 43-46). NFPA is associated with increased mortality: recent studies show a standardized mortality ratio (SMR) ranging from 1.1 (95% CI, 1.00-1.20) in Sweden (43) to 3.6 (2.9–4.5) in the UK (16). Only older age was associated with mortality in the multivariate analysis of this latter study. Gender might also have

an impact, as mortality is higher in women, but has been reported to improve in recent years (47) Cardiovascular morbidity might be increased, mainly driven by a higher incidence of cerebrovascular infarctions, especially in patients who had received radiotherapy (48, 49).

CLINICAL PRESENTATION

Clinical signs and symptoms (Figure 1)

Mass effects

The vast majority of NFPAs, whether hormonally active (i.e. gonadotropin-secreting or silent lactotroph, somatotroph or corticotroph adenomas) or inactive (null-cell adenomas), are revealed by mass effects on anatomic structures in the vicinity of the pituitary (headache, optic chiasm compression in 40-70% of cases, occasional cranial nerve III, IV and VI compression) and/or on pituitary hormonal function, leading to hypopituitarism (16, 43-45, 50). Hypopituitarism can be caused by anterior pituitary compression, pituitary stalk interruption, or hypothalamic involvement. Sequential loss of hormone secretion usually begins with GH or gonadotropins; decrease in TSH and ACTH secretion may follow (51). Pituitary stalk compression can also produce hyperprolactinemia, by disinhibiting the dopaminergic tone that normally acts at the level of pituitary lactotrophs, causing amenorrhea and galactorrhea, but PRL serum levels are always below 150-200 ng/ml (45, 52). This distinguishes them from macroprolactinomas, which are associated with much higher PRL levels, proportional to tumor size (53-55).

Pituitary apoplexy

Pituitary apoplexy may be the presenting feature of NFPA, with severe headaches of sudden onset, meningismus, a variably depressed sensorium, and visual disturbances (56). Between 2% and 12% of patients with all types of adenoma experience apoplexy, and the diagnosis of pituitary tumor was unknown at time of apoplexy in more than 3 out of 4 cases (56). In conservatively managed NFPA the risk of pituitary apoplexy was calculated to be between 0.2 and 0.6 events per 100 person-years in 2 metaanalyses (57, 58).

Hyperstimulation syndromes (59)

Very rarely, gonadotropin hypersecretion can stimulate the gonads: macro-orchidism has been reported in males (19, 21) and an ovarian hyperstimulation syndrome in premenopausal women with FSH-secreting tumors (17, 18, 20, 60, 61) .

Incidentalomas

An increasing proportion of pituitary tumors (up to 15% of NFPA) are detected by chance on computed tomography (CT) or magnetic resonance imaging (MRI) of the brain performed for unrelated reasons (62-65). These tumors are called pituitary incidentalomas. In their great majority they are smaller than 1 cm diameter and non functioning. Macroadenoma account for only about 1% of incidentalomas (66). After careful hormonal and neuro-radiological evaluation, the main issues in these patients is to know If a pituitary macroadenoma will grow or remain unchanged, in order to manage them adequately (67). Macroadenomas have a greater tendency to grow than microadenomas (12.5% of patients per year vs. 3.3%) and solid lesions show greater progression than cystic ones (5.7% of patients per year vs. 0.05%) (57, 68). In a series of 115 NF incidentalomas, growth was reported in 20% of cases at 4

years (57, 68). In a review of 353 macroincidentalomas (69), increase and decrease in size was observed in 24% and 12%, respectively; the rate of increase increased with the length of follow-up: 17% for follow-up < 4 years (38/215) and 34% for follow-up 5–8 years (47/138). On the other hand, the natural history of NFPAs microadenoma is likely to be benign and does not necessitate close follow up by MRI (70).

BIOCHEMICAL EVALUATION

Gonadotropins and subunit secretion

When a functioning adenoma produces an excess hormone (e.g. GH or ACTH) a clinical syndrome (e.g. acromegaly or Cushing syndrome) is observed, and the diagnosis is readily confirmed by hormone assays (71). By definition, this important clinical marker is generally lacking in patients with NFPA. As already mentioned, the vast majority of NFPAs are gonadotroph, i.e. able to produce gonadotropins or their subunits. However, baseline plasma dimeric FSH and/or LH levels are rarely elevated [see (72, 73) for review]. Elevation of free subunit levels (mainly alpha LH, more rarely beta LH) is more common but is generally moderate.

About 50% of male and about 30% of premenopausal female gonadotroph adenoma patients have excess secretion of FSH, LH or their free subunits, in a sufficient amount for measurement in serum (72, 74-76). In the postmenopausal state, assessing the secreting status is more difficult because of the physiological elevation of gonadotropins and subunits levels. Increased FSH levels in post-menopausal women, in combination with low LH levels and low levels of all pituitary hormones can help to preoperatively diagnose a gonadotroph adenoma (72).

TRH and GnRH stimulation tests to measure the response of gonadotropins is no longer recommended, as these tests are neither sensitive nor specific for indicating the gonadotroph nature of NFPA (73) and can also trigger rarely pituitary apoplexy (56).

Other pituitary hormones

Patients with pituitary macroadenomas, whether discovered incidentally or revealed by a mass effect, require a careful assessment of all secreted pituitary hormones to exclude hypersecretion and to diagnose pituitary hormone deficiencies that may require preoperative replacement therapy.

The search for “silent” hypersecretion of other pituitary hormones.

The abnormal secretion of pituitary hormones such as ACTH, PRL or GH may be totally silent or subclinical (25). A silent corticotroph adenoma can be completely silent, but sometimes also revealed preoperatively by an elevated ACTH level concomitant with a normal morning cortisol level, or by a “paradoxically” normal cortisol level despite deficiency of all other pituitary hormones (73). An overnight dexamethasone suppression test may be contributory and free urinary cortisol might be elevated (77).

By definition, IGF-I levels are normal in patients with a silent somatotroph adenoma; if they are not normal, then acromegaly should be diagnosed, even in the absence of clear clinical signs (78).

PRL is also routinely measured in patients with NFPA. If the PRL levels are only moderately elevated and do not correspond to the adenoma size, hyperprolactinemia is likely the result of pituitary stalk compression (see above). It might be kept in mind

that a PRL assay artifact called “hook effect” can mask very high levels of PRL (79, 80) and could falsely orientate the diagnosis to hyperprolactinemia related to stalk compression. This should be excluded by the measurement of PRL in 1/10 to 1/100-diluted serum (81).

Screening for hypopituitarism

At the time of NFPA diagnosis, 60% to 85% of patients have at least one pituitary hormone deficiency. Gonadotropic deficiency is the most prevalent (>80% of cases), followed by somatotropic deficiency. Thyrotropic and corticotropic deficiencies are found in 20-50% of cases (50, 73, 82-86).

PREOPERATIVE ASSESMENT

Pituitary imaging

Neuroradiological assessment of NFPA is based on MRI (73, 87, 88). On MRI, NFP macroadenomas appear as a mass centered on an enlarged sella turcica, with T1/T2 signal variations due to necrotic and/or hemorrhagic areas, and possibly with a fluid level. Tumor enhancement is usually only weak (Figure 2). The tumor may extend upwards, toward the optic pathways, laterally into the cavernous sinuses (internal carotid artery encasement is a sign of cavernous sinus invasion while visualization of the medial cavernous sinus veins indicates the absence of invasion) and/or downwards into the sphenoid sinus, with lysis of the sellar floor. If discovered incidentally, it has to be differentiated from other pituitary lesions (67, 88).

Ophthalmologic assessment of NFPA patients

NFPAs are a major source of visual disorders (16, 43-46), and are diagnosed later than functioning adenomas, often with larger tumor volume. Patients may be unaware of their visual deficit, especially in case of bitemporal hemianopsia, as the functioning visual field in one eye can compensate the visual field loss in the other eye.

Neuro-ophthalmologic exploration is one of the main factors guiding the surgical decision. Ophthalmologic assessment includes sensory evaluation with measurement of visual acuity (VA) and visual field examination (VF), preferably using a central static + peripheral kinetic approach. Anterior segment and fundus examinations are also essential for interpreting the VA and VF data. Optic nerve optical coherence tomography (OCT) is contributory but not essential for estimating the visual prognosis (89).

GENERAL PRINCIPLES OF TREATMENT

The choice of treatment is determined by i) the need for immediate relief from a mass effect or hormonal abnormalities, ii) the chance of long-term tumor control and iii) life expectancy and co-morbidities of the patient.

Surgery and radiotherapy are the two radical treatment options. A conservative approach may be appropriate for patients with an incidentally discovered pituitary adenoma ("incidentaloma"), provided the tumor is small, well defined, non-secreting and has no suprasellar or lateral extension (risk of neurological or visual chiasm compression).

Patient management of pituitary incidentalomas differ from that of symptomatic pituitary adenomas (62-65, 90). If the adenoma is at distance to the optic chiasma, radiological follow up by MRI should be performed after 6-12 months together with a

hormonal biochemical assessment looking for hypopituitarism (65, 87) (63). In case of absence of progression, surveillance intervals may be increased. If the adenoma is close to the optic chiasm, the French Endocrine Society Consensus (65, 87) considers that surgery is not formally indicated but should be discussed with the patient, taking into account the natural history of NFPA, the low morbidity associated with surgery, and the need for the patient's compliance with surveillance, any plans for pregnancy, and risk factors for apoplexy, etc. If surgery is not decided on, control MRI should be performed at 6 months, completed by hormonal and visual assessment. MRI and hormonal assessment are thereafter continued annually, with visual evaluation every 6 months.

A watchful waiting strategy may also be considered if surgery is contraindicated or declined.

THE RESULTS OF SURGICAL TREATMENT OF NON FUNCTIONING PITUITARY ADENOMAS

Surgery is generally the first-line treatment for NFPAs, usually *via* a trans-sphenoidal approach (91).

Remission is defined as the disappearance of visible tumor on MRI after total surgical removal. The average remission rate after surgery is between 20% (95% CI: 12-57) according to one meta-analysis (84), and 47.3% (range, 3-92) at one year according to another (92).

Visual function improves (partially or fully) after surgery in 80–90% of cases (93-95). Visual recovery may be very gradual, continuing up to one year after surgery. Some studies have shown a correlation between the degree of visual recovery and the duration and severity of ophtamologic disorders. Visual acuity <0.1 and optic atrophy

both carry a poor visual prognosis (83, 96). Visual disorders are thus an indication for surgery, even though complete recovery cannot be guaranteed.

The risk of onset of further **pituitary deficiencies** in patients with pituitary macroadenomas has been estimated at 12% per year (91). Arafah et al. found that preoperative deficiencies, headache and hyperprolactinemia significantly influenced the chances of postoperative recovery: when all the criteria were met (which suggests an increased intrasellar pressure), deficiencies and headache were more likely to improve postoperatively (97, 98). Surgery normalized anterior pituitary function in about 20-50% of cases after an average follow-up of one year (51, 84, 86, 99) and the rate is higher with earlier management. This explains why some authors recommend surgery even if the macroadenoma is asymptomatic (99).

The risk of a postoperative deterioration in pituitary function is 1-10% (51, 86, 92, 94, 95). Transcranial excision gives much poorer results (51, 84). The risk of postoperative onset of diabetes insipidus is less than 5%.

Headache is classically attributed to distension of the dural envelopes (84). Headache due to a mass effect is generally relieved by surgery (83, 100, 101). However, patients should be informed that relief cannot be guaranteed as causality is unproven.

Difficult situations

NFPAs in elderly patients: NFPAs account for 60–80% of pituitary adenomas occurring in the elderly, with an annual incidence of around 7/100 000 (102-104). The main presenting symptom, as in younger patients, is visual impairment (50–70% of cases) (103). Most macroadenomas have a maximal diameter of 2–4 cm at diagnosis (103). Management decisions must take account the visual impact, tumor proximity to

the chiasm, and comorbidities (103). However, mortality is not higher than in the general population (<1%) if the anesthetic risk is well controlled (103) and if the transphenoidal route is preferred to the transcranial approach (84). The rates of recovery from visual disorders and pituitary deficiency are similar to those obtained in young patients, despite a larger tumor size at time of pituitary surgery in elderly patients (105). The indications are the same in elderly patients as in younger patients, provided that relevant comorbidities, the anesthetic risk and the real impact to the patient are taken into account.

The surgical decision is more difficult in **patients taking antiplatelet drugs or anticoagulants**. Indeed, patients on long-term anticoagulant or antiplatelet therapy have a higher risk of postoperative hemorrhagic complications. However, preoperative drug withdrawal (5 days ahead of surgery for aspirin and vitamin K antagonists and, ideally, 10 days for clopidogrel) is associated with increased morbidity and mortality, especially in patients with active stents (91).

Surgical technique: microsurgery or endoscopy?

More than the technique itself, it is the neurosurgeon's experience that determines outcome. Endoscopy may be preferable to microscopy, as it offers better control of lateral and superior tumor extension but in terms of surgical outcome, both techniques are comparable (106, 107). The complications rate seems similar, e.g. worsening of visual and pituitary functions in 2.4 and 13.7% cases, respectively, and persistent diabetes insipidus in 6.2% cases with an endoscopic approach, comparable to the microscopic approach in a recent study (108).

POSTOPERATIVE MANAGEMENT OF PATIENTS WITH NON FUNCTIONING PITUITARY ADENOMAS

Despite progress in neurosurgery, the size and frequent invasiveness of NFPA often results in partial resection (see above), and the remnant (present in 50-80% of cases) may regrow (84, 92, 109, 110). Recurrence is also possible, although rare, even when total resection has been achieved (84, 92, 109, 111). Adjuvant therapy (surgical revision, radiation therapy, medications) may be indicated in case of tumor remnant progression. Otherwise, a watchful waiting strategy is preferable (Figure 3) (87).

Factors involved in NFPA recurrence

Several recent meta-analyses (84, 92, 111) have shown that recurrence rate is higher in NFPA than in secreting adenomas, with little change over the past 30 years (92).

Clinical factors

The best-identified factor for recurrence is the presence of a postoperative adenoma remnant (Table 1). After apparently complete resection confirmed by MRI, the risk of recurrence is around 10–20% and 30%, five and ten years after surgery, respectively (44, 45, 84, 92, 110-122). In two meta-analysis, the mean recurrence rate in patients **without** a visible tumor residue was 11-12% (92, 111); the postoperative remission rate was 96% and 82% at five and ten years, respectively (111); and most recurrences were diagnosed between one and 10 years postoperatively (92). In patients **with** a postoperative tumor remnant, the recurrence rate was 25-40% and 50-60%, five and ten years after surgery, respectively (44, 45, 84, 92, 111-122).

According to a meta-analysis, the mean recurrence rate was 46% in patients with a tumor residue; progression-free survival among these patients was 56% and 40% at 5 and 10 years, respectively; and the mean residual tumor volume doubling time was 3.4 years (111).

Tumor invasiveness might be another predictor for a post-operative tumor residual or recurrence, although its prognostic value on long-term recurrence is conflicting (38, 123-125).

Other clinical factors including a younger age, gender and initial tumor size had prognostic significance in some studies but not in others (92). In silent corticotroph adenomas, less cystic tumors and higher ACTH levels might be indicators for recurrence (126). In addition, texture parameters on pre-operative MRI examinations be predictive (127).

Histologic factors

The prognosis is classically poorer in case of a silent corticotroph adenoma [rev. in (109)]. As in other types of pituitary adenoma, expression of tumor biomarkers, particularly Ki-67, a high mitotic count and strong p53 expression (see above) can help to assess the risk of recurrence (13, 36, 128, 129).

Other prognostic factors might include an upregulation of minichromosome maintenance falchproteins (130) and gene expression profiles (131).

According to a prognostic classification, which combines tumor invasiveness and markers of proliferation, a grade 2b (i.e. invasive and proliferative) gonadotroph tumors are associated with a 7.5 higher risk of recurrence or progression compared

to grade 1a (i.e. non-invasive and non-proliferative) (36, 39, 124). This has been confirmed in independent series (38).

Postoperative follow-up

MRI and ophthalmologic monitoring

Usually, the first postoperative MRI is performed after 3 or 6 months. If no tumor remnant is present, the French Endocrine Society Consensus recommends yearly MRI follow-up for 5 years, then at 7, 10 and 15 years. If a remnant is present, MRI may be repeated annually for 5 years and then every 2 or 3 years in the absence of progression. The schedule is then redefined on a case-by-case basis, according to the size of the remnant and its distance from the optic pathways (87, 109). If visual defects persist preoperatively, visual assessment should be performed regularly until the maximal improvement is achieved.

Hormonal follow-up

Biochemical hormonal assessment 3 months after surgery shows whether the preoperative pituitary deficiencies have improved and if any new deficiencies have occurred. Biochemical exploration is then repeated for adaptation of replacement therapies. If radiotherapy is decided, pituitary function needs to be assessed every year in order to detect possible late-onset deficiencies.

Options in case of tumor recurrence or remnant progression

Repeat surgery

Repeat surgery (118, 119) may be indicated if the growing residue or recurrence is amenable to total resection, if optic pathway compression persists or recurs, or if surgery can help to achieve the anatomic conditions necessary for stereotactic radiotherapy (3–5 mm safety margin between the adenoma and optic pathways). However, repeat surgery is less effective in terms of tumor control (it often persists a remnant) and visual outcome, and complications (CSF leak) are more frequent than after initial surgery (132, 133).

Radiation therapy (RT)

The type of RT applied mainly depends on the size of the tumor remnant, as well as on its distance to the optic pathways. Conventional (fractionated conformal RT) and modern (radiosurgery and fractionated stereotactic RT) RT appear to be similarly effective for local tumor control (134).

Postoperative **fractionated RT** considerably reduces the risk of NFPA recurrence, with a 10-year progression-free survival rate higher than 90% in most series (45, 111, 117, 132, 135-139) (Table 2). Almost all reports show a major benefit of RT in terms of the non-recurrence rate at 5 years ($66\pm 19\%$ without RT, $94\pm 9\%$ with RT) and at 10 years ($52 \pm 16\%$ and $92 \pm 6\%$, respectively). The overall relapse rate was about 3-fold lower with RT (55/468, 12% with RT; 321/986, 32% without RT). A meta-analysis (84) showed a relative risk of recurrence of 1.97 without RT compared with RT.

Studies of **fractionated stereotactic RT** have involved fewer patients, and mean follow-up rarely exceeds 5 years (140-147). The results are generally similar to those of classical RT, with tumor control in more than 95% of patients at 5 years and in more than 90 % of cases at 10 years.

Studies of **radiosurgery** also involved small numbers of patients, with less than 10 years of follow-up (148-162). The results are generally similar to those of fractionated RT, with tumor control in 90–100% of patients at 5 years. Data for 512 patients managed in nine North American centers showed tumor control rates of 95% and 85% at 5 and 10 years, respectively (160). A meta-analysis showed better tumor control in patients with tumors smaller than 4 ml (163).

Despite this clear evidence on tumor control, the general use of RT is limited by unwanted side effects of radiation toxicity occurring in the long term follow up especially after the use of higher doses. Tumor growth as such might only be an outcome parameter of limited value, since not the size of a NFPA itself, but rather the effects on visual function, mortality or quality of life are of clinical relevance. However, studies investigating the benefits and risks of RT prospectively in long-term follow up are missing (134).

Hypopituitarism is the most frequent complication and may occur after several years and progress with time. Its prevalence ranges from 50% to 80% and increases with the time of follow-up (132). Regular long-term follow-up of pituitary function is thus mandatory after RT.

Studies on visual outcomes after RT are scarce. Severe ophthalmologic complications are rare (<1%), and may occur late (164). Following radiosurgery, the incidence of visual impairment ranges from 0 to 13.7%, depending on the series. (148-162).

They are more frequent when optic pathway was already impaired prior to RT and when systematic prospective ophthalmological follow up is organized after fractionated stereotactic RT (146).

Radiation-induced brain tumors (astrocytoma, glioma, glioblastoma sarcoma or meningioma) are a rare but well-established risk of RT: in a series of 426 adenomas treated with RT between 1962 and 1994, the risk was 2% at 10 years, 2.4% at 20 years and 8.5% at 30 years (165).

Vascular inflammation secondary to RT may induce or aggravate atherosclerosis, which can also be aggravated by hypopituitarism and its treatment (e.g. overtreatment with glucocorticoids). An increased risk of stroke and cardio/cerebrovascular death has been found in patients with hypopituitarism treated by radiotherapy (166-169).

Given its potential side effects, most experts now agree that immediate postoperative RT is not indicated after complete tumor resection, as the risk of recurrence is low (134). Treatment can be postponed without loss of efficacy, but regular MRI surveillance should be maintained for many years. In case of recurrence, RT might be proposed, preceded or not by a repeat surgery (see above).

In the presence of a significant tumor residue, especially if invasive, the indications for RT should take into account risk factors for tumor regrowth, the patient's age and history, and the presence of hypopituitarism. In most cases, regular monitoring is an acceptable option, treatment being postponed until the residue progresses and/or becomes threatening. RT is indicated if the tumor has a high growth potential, and the tumoral risk always takes precedence over hypopituitarism when considering management options.

The different RT modalities have similar efficacy in terms of tumor control, and the choice thus depends on the size, boundaries and location of the tumor residue with

respect to neighboring neural structures, and also on the center's experience with and access to the different machines.

Medical treatment

Given the high prevalence of tumor remnant regrowth in long-term follow up, as well as the above-mentioned side effects of repeated pituitary surgery and RT, a medical therapy for NFPA is urgently needed (170). Based on the available evidence, a therapeutic trial with cabergoline might be considered for progressing NFPA. However, its routine use is conflicting (171). dopamine agonists have been reported to reduce NFPA volume (172) and preventive dopamine agonists therapy might reduce the risk of residual tumor enlargement during follow up, in retrospective (173) and prospective randomized studies (174). The available retrospective studies used variable drug doses and treatment durations (175) and outcome measures were not related to NFPA D2 receptors abundance (173). However, the rather small sample size, the length of the follow up and potential differences in invasiveness and proliferation characteristics between the intervention and control group were important limitations of studies investigating the effects of dopamine agonists on NFPA's growth (171). A recent randomized, parallel, open-label clinical trial compared cabergoline with nonintervention in patients with residual NFPA after transsphenoidal surgery over 2 years and showed that, at the end of the study, residual tumor shrinkage, stabilization, and enlargement were observed in 28.8%, 66.1%, and 5.1% of patients, respectively, in the cabergoline group and in 10.5%, 73.7%, and 15.8% of patients, respectively, in the control group ($P=0.01$) (174). D2R was not associated with cabergoline responsiveness.

Gn-RH agonists and antagonists have proved unable to reduce the volume of NFPAs (175).

Somatostatin analogs were reported to reduce tumor volume in a small percentage of cases (175), without effects on visual field and pituitary function.

CONCLUSION

NFPA is usually diagnosed in a patient with signs and symptoms related to a mass effect. Patient management is summarized in Figure 3. Unless contraindicated, and in a few particular situations, surgery is the mainstay of treatment, after detailed hormonal, neuroradiologic and ophthalmologic assessment. Resection, generally *via* a trans-sphenoidal approach (with the help of an endoscope), should be performed by a neurosurgeon with extensive experience in pituitary surgery, in order to maximize the chances of complete resection and to minimize complications. If a tumor remnant persists (a frequent situation in patients with large and often invasive adenomas), watchful waiting is preferred to routine radiotherapy, as long as the tumor residue does not grow. NFPA can sometimes recur even after complete resection. Postoperative irradiation is only considered in case of residual tumor growth or relapse. Non-functioning pituitary incidentalomas may, because of their fortuitous discovery, require a different approach, especially when they are small and/or remote from the optic pathways.

Figure legends

Figure 1. NFPA presenting symptoms and signs [adapted from (45)]

Figure 2. Sagittal (A) and coronal, before (B) and after gadolinium injection (C) views of a NFPA with suprasellar extension.

Figure 3. Proposed NFPA patient management

Table I: Results of surgery and risk of recurrence according to postoperative remnant status; RT, radiotherapy; PFS, progression-free survival; * defined as a remnant <1 cm, ** defined as a remnant >1 cm

First author (Year)	Ref	Patient total / patients without RT	Follow-up (years)	Type of study	Recurrence in the absence of remnant	Recurrence in the presence of remnant
Turner (1999)	(112)	65/65	6.3	retrospective	9/31 (20%)	12/34 (35%)
Woolons (2000)	(113)	72/22	5.3	retrospective	2/11 (18%)	8/11 (73%)
Soto-Ares (2002)	(114)	51/51	5.6	prospective	0/17 (0%)	13/34 (38%)
Greenman (2003)	(115)	122/108	4.2	prospective	6/30 (20%)	41/78 (53%)
Ferrante (2006)	(44)	226/150	8.1	retrospective	14/73 (19%)	45/77 (58%)
Dekkers (2006)	(116)	97/91	6	retrospective	1/27 (4%)	9/64 (14%)
Van den Bergh (2007)	(117)	122/46	8	retrospective	1/18 (6%)	16/28 (57%)
Losa (2008)	(118)	436/355	4.5	prospective	PFS 5 years: 87.1%	PFS 5 ans: 39.2%
O'Sullivan (2009)	(119)	126/126	5.7	retrospective	0/26 (0%)	53/100 (53%)
Brochier (2010)	(45)	142/127	6.9	retrospective	10/42 (24%)	46/85 (54%)

Reddy (2011)	(120)	144/144	6.1	retrospective	2/29 (7%)	49/115 (43%)
Maletkovic (2019)	(110)	93/85	3	retrospective	2/59 (3%)	8/22 (36%)
Total		1696/1370			47/363 (13%)	300/648 (46%)

Table 2. Impact of fractionated conformational radiotherapy (FRT) on the risk of NFPA progression/recurrence in recent series

First author (year)	Ref.	N	Follow-up (years)	N patients with FRT/ N patients without FRT	% free of recurrence at 5 years		% free of recurrence at 10 years	
					FRT	No FRT	FRT	No FRT
Jaffrain-Rea (1993)	(136)	57	7.1	24/33	100%	70 %	96%	55%
Gittoes (1998)	(135)	126	9	81/355	93%	68%	93%	47%
Woollons (2000)	(113)	72	5.3	50/22	72%	34%	-	-
Park (2004)	(138)	176	4.3	44/132	98%	85%	98%	50%

Van den Bergh (2007)	(117)	122	8	76/46	95%	49%	95%	22%
Olsson (2009)	(137)	235	10	62/173	-	-	94%	62%
Brochier (2010)	(45)	142	6.9	15/127	100%	70%	91%	52%

References

1. Snyder PJ, Sterling FH. Hypersecretion of LH and FSH by a pituitary adenoma. *J Clin Endocrinol Metab.* 1976;42:544-50.
2. Kovacs K, Horvath E, Van Loon GR, Rewcastle NB, Ezrin C, Rosenbloom AA. Pituitary adenomas associated with elevated blood follicle-stimulating hormone levels: a histologic, immunocytologic, and electron microscopic study of two cases. *Fertil Steril.* 1978;29(6):622-8.
3. Beckers A, Stevenaert A, Mashiter K, Hennen G. Follicle-stimulating hormone-secreting pituitary adenomas. *J Clin Endocrinol Metab.* 1985;61:525-8.
4. Trouillas J, Girod C, Sassolas G, Claustrat B, Lheritier M, Dubois MP, et al. Human pituitary gonadotropic adenoma; histological, immunocytochemical, and ultrastructural and hormonal studies in eight cases. *J Pathol.* 1981;135(4):315-36.
5. Jameson JL, Klibanski A, Black PM, Zervas NT, Lindell CM, Hsu DW, et al. Glycoprotein hormone genes are expressed in clinically nonfunctioning pituitary adenomas. *J Clin Invest.* 1987;80:1472-8.
6. Yamada S, Asa SL, Kovacs K, Muller P, Smyth HS. Analysis of hormone secretion by clinically nonfunctioning human pituitary adenomas using the reverse hemolytic plaque assay. *J Clin Endocrinol Metab.* 1989;68(1):73-80.
7. Asa SL. Pituitary adenomas. In: Asa SL, editor. *Tumors of the Pituitary Gland. Fourth Series Fascicle 15.* Washington, DC: Armed Forces Institute of Pathology; 2011. p. 55–172.
8. Asa SL, Cheng Z, Ramyar L, Singer W, Kovacs K, Smyth HS, et al. Human pituitary null cell adenomas and oncocytomas in vitro: effects of

adenohypophysiotropic hormones and gonadal steroids on hormone secretion and tumor cell morphology. *J Clin Endocrinol Metab.* 1992;74(5):1128-34.

9. Lloyd RV, Kovacs K, Young JWF, Farrel WE, Asa, S. L., Trouillas J, Kontogeorgos G, et al. Tumours of the pituitary. In: DeLellis RA, Lloyd RV, Heitz PU, Eng C, editors. *Pathology and genetics of tumours of endocrine organs. WHO/IARC Classification of Tumours*,. 8. 3rd ed. Lyon, France: IARC Press; 2004. p. 1-50.

10. Black PM, Jameson JL, Hsu DN, Klibanski A, Hedley-Whyte ET, Ridgway EC, et al. Hormone products of apparently non functioning pituitary adenomas. In: Landolt AM, Heitz PU, Zapf J, Girard J, Del Pozo E, editors. *Advances in Pituitary Adenoma Research.* 69. Oxford: Pergamon Press; 1988. p. 413.

11. 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(1):42-57.

12. Asa SL, Bamberger AM, Cao B, Wong M, Parker KL, Ezzat S. The transcription activator steroidogenic factor-1 is preferentially expressed in the human pituitary gonadotroph. *J Clin Endocrinol Metab.* 1996;81(6):2165-70.

13. Mete O, Asa SL. Clinicopathological correlations in pituitary adenomas. *Brain Pathol.* 2012;22(4):443-53.

14. Nishioka H, Inoshita N, Mete O, Asa SL, Hayashi K, Takeshita A, et al. The Complementary Role of Transcription Factors in the Accurate Diagnosis of Clinically Nonfunctioning Pituitary Adenomas. *Endocr Pathol.* 2015;26(4):349-55.

15. Kobalka PJ, Huntoon K, Becker AP. Neuropathology of Pituitary Adenomas and Sellar Lesions. *Neurosurgery.* 2021;88(5):900-18.

16. Ntali G, Capatina C, Fazal-Sanderson V, Byrne JV, Cudlip S, Grossman AB, et al. Mortality in patients with non-functioning pituitary adenoma is increased:

systematic analysis of 546 cases with long follow-up. *Eur J Endocrinol*. 2015;174(2):137-45.

17. Graillon T, Castinetti F, Chabert-Orsini V, Morange I, Cuny T, Albarel F, et al. Functioning gonadotroph adenoma with severe ovarian hyperstimulation syndrome: A new emergency in pituitary adenoma surgery? Surgical considerations and literature review. *Ann Endocrinol (Paris)*. 2019;80(2):122-7.

18. Caretto A, Lanzi R, Piani C, Molgora M, Mortini P, Losa M. Ovarian hyperstimulation syndrome due to follicle-stimulating hormone-secreting pituitary adenomas. *Pituitary*. 2017;20(5):553-60.

19. Heseltine D, White MC, Kendall-Taylor P, de Kretser DM, Kelly W. Testicular enlargement and elevated serum inhibin concentrations occur in patients with pituitary macroadenomas secreting follicle-stimulating hormone. *Clin Endocrinol*. 1989;31:411-23.

20. Kawaguchi T, Ogawa Y, Ito K, Watanabe M, Tominaga T. Follicle-stimulating hormone-secreting pituitary adenoma manifesting as recurrent ovarian cysts in a young woman--latent risk of unidentified ovarian hyperstimulation: a case report. *BMC Res Notes*. 2013;6:408.

21. Dahlqvist P, Koskinen LO, Brannstrom T, Hagg E. Testicular enlargement in a patient with a FSH-secreting pituitary adenoma. *Endocrine*. 2010;37(2):289-93.

22. Pigny P, Henric B, Lahlou N, Christin S, Mazzuca M, Dewailly D, et al. A gonadotroph adenoma with a high proportion of basic FSH isohormones by chromatofocusing. *J Clin Endocrinol Metab*. 1996;81(6):2407-8.

23. Galway AB, Hsue AJW, Daneshdoost L, Zhou MH, Pavlou SN, Snyder PJ. Gonadotroph adenomas in men produce biologically active follicle-stimulating hormone. *J Clin Endocrinol Metab*. 1990;71:907-12.

24. Borgato S, Romoli R, Cortelazzi D, Asteria C, Persani L, Beck-Peccoz P. FSH bioactivity and serum inhibin a- α and a- β a levels in patients with gonadotropinoma and non functioning pituitary adenomas. *J Endocrinol Invest.* 1996;19 (Suppl to 5):34 (Abstract).
25. Drummond J, Roncaroli F, Grossman AB, Korbonits M. Clinical and Pathological Aspects of Silent Pituitary Adenomas. *J Clin Endocrinol Metab.* 2019;104(7):2473-89.
26. Mete O, Lopes MB. Overview of the 2017 WHO Classification of Pituitary Tumors. *Endocr Pathol.* 2017;28(3):228-43.
27. Raverot G, Wierinckx A, Jouanneau E, Auger C, Borson-Chazot F, Lachuer J, 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(1):35-43.
28. Erickson D, Scheithauer B, Atkinson J, Horvath E, Kovacs K, Lloyd RV, et al. Silent subtype 3 pituitary adenoma: a clinicopathologic analysis of the Mayo Clinic experience. *Clin Endocrinol (Oxf).* 2009;71(1):92-9.
29. Kovacs K, Lloyd R, Horvath E, Asa SL, Stefanescu L, Killinger DW, 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(2):345-53.
30. Trouillas J, Sassolas G, Loras B, Velkeniers B, Raccurt M, Chotard L, et al. Somatotrophic adenomas without acromegaly. *Pathol Res Pract.* 1991;187(8):943-9.
31. Mete O, Gomez-Hernandez K, Kucharczyk W, Ridout R, Zadeh G, Gentili F, et al. Silent subtype 3 pituitary adenomas are not always silent and represent poorly

differentiated monomorphous plurihormonal Pit-1 lineage adenomas. *Mod Pathol.* 2016;29(2):131-42.

32. Trouillas J, Labat-Moleur F, Sturm N, Kujas M, Heymann MF, Figarella-Branger D, 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(4):534-43.

33. Le Bras M, Leclerc H, Rousseau O, Goudet P, Cuny T, Castinetti F, et al. Pituitary adenoma in patients with multiple endocrine neoplasia type 1 - a cohort study. *Eur J Endocrinol.* 2021.

34. Al-Salameh A, Cadiot G, Calender A, Goudet P, Chanson P. Clinical aspects of multiple endocrine neoplasia type 1. *Nat Rev Endocrinol.* 2021;17(4):207-24.

35. Raverot G, Burman P, McCormack A, Heaney A, Petersenn S, Popovic V, et al. European Society of Endocrinology Clinical Practice Guidelines for the management of aggressive pituitary tumours and carcinomas. *Eur J Endocrinol.* 2018;178(1):G1-G24.

36. Trouillas J, Roy P, Sturm N, Dantony E, Cortet-Rudelli C, Viennet G, 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(1):123-35.

37. Asioli S, Righi A, Iommi M, Baldovini C, Ambrosi F, Guaraldi F, et al. Validation of a clinicopathological score for the prediction of post-surgical evolution of pituitary adenoma: retrospective analysis on 566 patients from a tertiary care centre. *Eur J Endocrinol.* 2019;180(2):127-34.

38. Lelotte J, Mourin A, Fomekong E, Michotte A, Raftopoulos C, Maiter D. Both invasiveness and proliferation criteria predict recurrence of non-functioning pituitary

macroadenomas after surgery: a retrospective analysis of a monocentric cohort of 120 patients. *Eur J Endocrinol.* 2018;178(3):237-46.

39. Raverot G, Ilie MD, Lasolle H, Amodru V, Trouillas J, Castinetti F, et al. Aggressive pituitary tumours and pituitary carcinomas. *Nat Rev Endocrinol.* 2021;17(11):671-84.

40. Raappana A, Koivukangas J, Ebeling T, Pirila T. Incidence of pituitary adenomas in Northern Finland in 1992-2007. *J Clin Endocrinol Metab.* 2010;95(9):4268-75.

41. Daly AF, Rixhon M, Adam C, Dempegioti A, Tichomirowa MA, Beckers A. High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. *J Clin Endocrinol Metab.* 2006;91(12):4769-75.

42. Fernandez A, Karavitaki N, Wass JA. Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). *Clin Endocrinol (Oxf).* 2009.

43. Olsson DS, Nilsson AG, Bryngelsson IL, Trimpou P, Johannsson G, Andersson E. Excess Mortality in Women and Young Adults With Nonfunctioning Pituitary Adenoma: A Swedish Nationwide Study. *J Clin Endocrinol Metab.* 2015;100(7):2651-8.

44. Ferrante E, Ferraroni M, Castrignano T, Menicatti L, Anagni M, Reimondo G, et al. Non-functioning pituitary adenoma database: a useful resource to improve the clinical management of pituitary tumors. *Eur J Endocrinol.* 2006;155(6):823-9.

45. Brochier S, Galland F, Kujas M, Parker F, Gaillard S, Raftopoulos C, et al. Factors predicting relapse of nonfunctioning pituitary macroadenomas after neurosurgery: a study of 142 patients. *Eur J Endocrinol.* 2010;163(2):193-200.

46. Kanner AA, Corn BW, Greenman Y. Radiotherapy of nonfunctioning and gonadotroph adenomas. *Pituitary*. 2009;12(1):15-22.
47. Olsson DS, Bryngelsson IL, Ragnarsson O. Time trends of mortality in patients with non-functioning pituitary adenoma: a Swedish nationwide study. *Pituitary*. 2017;20(2):218-24.
48. Hammarstrand C, Ragnarsson O, Bengtsson O, Bryngelsson IL, Johannsson G, Olsson DS. Comorbidities in patients with non-functioning pituitary adenoma: influence of long-term growth hormone replacement. *Eur J Endocrinol*. 2018;179(4):229-37.
49. Tampourlou M, Fountas A, Ntali G, Karavitaki N. Mortality in patients with non-functioning pituitary adenoma. *Pituitary*. 2018;21(2):203-7.
50. Greenman Y, Stern N. Non-functioning pituitary adenomas. *Best Pract Res Clin Endocrinol Metab*. 2009;23(5):625-38.
51. Nomikos P, Ladar C, Fahlbusch R, Buchfelder M. Impact of primary surgery on pituitary function in patients with non-functioning pituitary adenomas -- a study on 721 patients. *Acta Neurochir (Wien)*. 2004;146(1):27-35.
52. Karavitaki N, Thanabalasingham G, Shore HC, Trifanescu R, Ansorge O, Meston N, et al. Do the limits of serum prolactin in disconnection hyperprolactinaemia need re-definition? A study of 226 patients with histologically verified non-functioning pituitary macroadenoma. *Clin Endocrinol (Oxf)*. 2006;65(4):524-9.
53. Klibanski A. Clinical practice. Prolactinomas. *N Engl J Med*. 2010;362(13):1219-26.
54. Rogers A, Karavitaki N, Wass JA. Diagnosis and management of prolactinomas and non-functioning pituitary adenomas. *BMJ*. 2014;349:g5390.

55. Chanson P, Maiter D. The epidemiology, diagnosis and treatment of Prolactinomas: The old and the new. *Best Pract Res Clin Endocrinol Metab.* 2019;33(2):101290.
56. Briet C, Salenave S, Bonneville JF, Laws ER, Chanson P. Pituitary Apoplexy. *Endocr Rev.* 2015;36(6):622-45.
57. Fernandez-Balsells MM, Murad MH, Barwise A, Gallegos-Orozco JF, Paul A, Lane MA, et al. Natural history of nonfunctioning pituitary adenomas and incidentalomas: a systematic review and metaanalysis. *J Clin Endocrinol Metab.* 2011;96(4):905-12.
58. Sivakumar W, Chamoun R, Nguyen V, Couldwell WT. Incidental pituitary adenomas. *Neurosurg Focus.* 2011;31(6):E18.
59. Ntali G, Capatina C, Grossman A, Karavitaki N. Clinical review: Functioning gonadotroph adenomas. *J Clin Endocrinol Metab.* 2014;99(12):4423-33.
60. Cooper O, Geller JL, Melmed S. Ovarian hyperstimulation syndrome caused by an FSH-secreting pituitary adenoma. *Nat Clin Pract Endocrinol Metab.* 2008;4(4):234-8.
61. Christin-Maitre S, Rongieres-Bertrand C, Kottler ML, Lahlou N, Frydman R, Touraine P, et al. A spontaneous and severe hyperstimulation of the ovaries revealing a gonadotroph adenoma [In Process Citation]. *J Clin Endocrinol Metab.* 1998;83(10):3450-3.
62. Chanson P, Young J. Pituitary incidentalomas. *The Endocrinologist.* 2003;13(2):124-35.
63. Freda PU, Beckers AM, Katznelson L, Molitch ME, Montori VM, Post KD, et al. Pituitary incidentaloma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2011;96(4):894-904.

64. Molitch ME. Nonfunctioning pituitary tumors and pituitary incidentalomas. *Endocrinol Metab Clin North Am.* 2008;37(1):151-71, xi.
65. Galland F, Vantyghem MC, Cazabat L, Boulin A, Cotton F, Bonneville JF, et al. Management of nonfunctioning pituitary incidentaloma. *Ann Endocrinol (Paris).* 2015;76(3):191-200.
66. Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML, et al. The prevalence of pituitary adenomas: a systematic review. *Cancer.* 2004;101(3):613-9.
67. Vasilev V, Rostomyan L, Daly AF, Potorac I, Zacharieva S, Bonneville JF, et al. MANAGEMENT OF ENDOCRINE DISEASE: Pituitary 'incidentaloma': neuroradiological assessment and differential diagnosis. *Eur J Endocrinol.* 2016;175(4):R171-84.
68. Sanno N, Oyama K, Tahara S, Teramoto A, Kato Y. A survey of pituitary incidentaloma in Japan. *Eur J Endocrinol.* 2003;149(2):123-7.
69. Molitch ME. Pituitary tumours: pituitary incidentalomas. *Best Pract Res Clin Endocrinol Metab.* 2009;23(5):667-75.
70. Han AJ, Varlamov EV, Fleseriu M. Non-Functioning Pituitary Microadenomas, Should Imaging Interval be Extended? A Large Single-Center Cohort Study. *J Clin Endocrinol Metab.* 2021.
71. Molitch ME. Diagnosis and Treatment of Pituitary Adenomas: A Review. *JAMA.* 2017;317(5):516-24.
72. Chanson P, Brochier S. Non-functioning pituitary adenomas. *J Endocrinol Invest.* 2005;28(11 Suppl):93-9.
73. Raverot G, Assie G, Cotton F, Cogne M, Boulin A, Dherbomez M, et al. Biological and radiological exploration and management of non-functioning pituitary adenoma. *Ann Endocrinol (Paris).* 2015;76(3):201-9.

74. Chanson P, Pantel J, Young J, Couzinet B, Bidart JM, Schaison G. Free luteinizing-hormone beta-subunit in normal subjects and patients with pituitary adenomas. *J Clin Endocrinol Metab.* 1997;82(5):1397-402.
75. Daneshdoost L, Gennarelli TA, Bashey HM, Savino PJ, Sergott RC, Bosley TM, et al. Recognition of gonadotroph adenomas in women. *N Engl J Med.* 1991;324:589-94.
76. Daneshdoost L, Gennarelli TA, Bashey HM, Savino PJ, Sergott RC, Bosley TM, et al. Identification of gonadotroph adenomas in men with clinically non functioning adenomas by the luteinizing hormone β subunit response to thyrotropin-releasing hormone. *J Clin Endocrinol Metab.* 1993;77:1352-5.
77. Ben-Shlomo A, Cooper O. Silent corticotroph adenomas. *Pituitary.* 2018;21(2):183-93.
78. Colao A, Grasso LFS, Giustina A, Melmed S, Chanson P, Pereira AM, et al. Acromegaly. *Nat Rev Dis Primers.* 2019;5(1):20.
79. Barkan AL, Chandler WF. Giant pituitary prolactinoma with falsely low serum prolactin: the pitfall of the "high-dose hook effect": case report. *Neurosurgery.* 1998;42(4):913-5; discussion 5-6.
80. Frieze TW, Mong DP, Koops MK. "Hook effect" in prolactinomas: case report and review of literature. *Endocr Pract.* 2002;8(4):296-303.
81. Binart N, Young J, Chanson P. Prolactin assays and regulation of secretion: animal and human data. In: Tritos NA, Klibanski A, editors. *Prolactin disorders From basic science to clinical management. Contemporary Endocrinology.* Springer Nature Switzerland AG: Humana Press; 2019. p. 55-78.
82. Greenman Y, Tordjman K, Kisch E, Razon N, Ouaknine G, Stern N. Relative sparing of anterior pituitary function in patients with growth hormone-secreting

macroadenomas: comparison with nonfunctioning macroadenomas. *J Clin Endocrinol Metab.* 1995;80(5):1577-83.

83. Dekkers OM, Pereira AM, Romijn JA. Treatment and follow-up of clinically nonfunctioning pituitary macroadenomas. *J Clin Endocrinol Metab.* 2008;93(10):3717-26.

84. Murad MH, Fernandez-Balsells MM, Barwise A, Gallegos-Orozco JF, Paul A, Lane MA, et al. Outcomes of surgical treatment for nonfunctioning pituitary adenomas: a systematic review and meta-analysis. *Clin Endocrinol (Oxf).* 2010;73(6):777-91.

85. Greenman Y, Stern N. How should a nonfunctioning pituitary macroadenoma be monitored after debulking surgery? *Clin Endocrinol (Oxf).* 2009;70(6):829-32.

86. Alexopoulou O, Everard V, Etoa M, Fomekong E, Gaillard S, Parker F, et al. Outcome of pituitary hormone deficits after surgical treatment of nonfunctioning pituitary macroadenomas. *Endocrine.* 2021;73(1):166-76.

87. Chanson P, Raverot G, Castinetti F, Cortet-Rudelli C, Galland F, Salenave S, et al. Management of clinically non-functioning pituitary adenoma. *Ann Endocrinol (Paris).* 2015;76(3):239-47.

88. Chapman PR, Singhal A, Gaddamanugu S, Prattipati V. Neuroimaging of the Pituitary Gland: Practical Anatomy and Pathology. *Radiol Clin North Am.* 2020;58(6):1115-33.

89. Abouaf L, Vighetto A, Lebas M. Neuro-ophthalmologic exploration in non-functioning pituitary adenoma. *Ann Endocrinol (Paris).* 2015;76(3):210-9.

90. Ntali G, Wass JA. Epidemiology, clinical presentation and diagnosis of non-functioning pituitary adenomas. *Pituitary.* 2018;21(2):111-8.

91. Castinetti F, Dufour H, Gaillard S, Jouanneau E, Vasiljevic A, Villa C, et al. Non-functioning pituitary adenoma: when and how to operate? What pathologic criteria for typing? *Ann Endocrinol (Paris)*. 2015;76(3):220-7.
92. Roelfsema F, Biermasz NR, Pereira AM. Clinical factors involved in the recurrence of pituitary adenomas after surgical remission: a structured review and meta-analysis. *Pituitary*. 2012;15(1):71-83.
93. 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(5):1006-15; discussion 15-7.
94. Tabae A, Anand VK, Barron Y, Hiltzik DH, Brown SM, Kacker A, et al. Endoscopic pituitary surgery: a systematic review and meta-analysis. *J Neurosurg*. 2009;111(3):545-54.
95. Tabae A, Anand VK, Barron Y, Hiltzik DH, Brown SM, Kacker A, et al. Predictors of short-term outcomes following endoscopic pituitary surgery. *Clin Neurol Neurosurg*. 2009;111(2):119-22.
96. 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(3):415-9.
97. 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(2):348-54.
98. 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(5):1789-93.

99. Messerer M, Dubourg J, Raverot G, Bervini D, Berhouma M, George I, et al. Non-functioning pituitary macro-incidentomas benefit from early surgery before becoming symptomatic. *Clin Neurol Neurosurg.* 2013;115(12):2514-20.

100. Comtois R, Beauregard H, Somma M, Serri O, Aris-Jilwan N, Hardy J. The clinical and endocrine outcome to transphenoidal microsurgery of non secreting pituitary adenomas. *Cancer.* 1991;68:860-6.

101. Yu B, Ji N, Ma Y, Yang B, Kang P, Luo F. Clinical characteristics and risk factors for headache associated with non-functioning pituitary adenomas. *Cephalalgia.* 2016.

102. 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(10):1091-5.

103. Minniti G, Esposito V, Piccirilli M, Fratticci A, Santoro A, Jaffrain-Rea ML. Diagnosis and management of pituitary tumours in the elderly: a review based on personal experience and evidence of literature. *Eur J Endocrinol.* 2005;153(6):723-35.

104. Turner HE, Adams CB, Wass JA. Pituitary tumours in the elderly: a 20 year experience. *Eur J Endocrinol.* 1999;140(5):383-9.

105. Villar-Taibo R, Diaz-Ortega C, Sifontes-Dubon M, Fernandez-Pombo A, Serramito-Garcia R, Martinez-Capoccioni G, et al. Pituitary surgery in elderly patients: a safe and effective procedure. *Endocrine.* 2021;72(3):814-22.

106. 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(8):843-9.
107. Bastos RV, Silva CM, Tagliarini JV, Zanini MA, Romero FR, Boguszewski CL, et al. Endoscopic versus microscopic transsphenoidal surgery in the treatment of pituitary tumors: systematic review and meta-analysis of randomized and non-randomized controlled trials. *Arch Endocrinol Metab*. 2016;60(5):411-9.
108. Magro E, Graillon T, Lassave J, Castinetti F, Boissonneau S, Tabouret E, et al. Complications Related to the Endoscopic Endonasal Transsphenoidal Approach for Nonfunctioning Pituitary Macroadenomas in 300 Consecutive Patients. *World Neurosurg*. 2016;89:442-53.
109. Cortet-Rudelli C, Bonneville JF, Borson-Chazot F, Clavier L, Coche Dequeant B, Desailoud R, et al. Post-surgical management of non-functioning pituitary adenoma. *Ann Endocrinol (Paris)*. 2015;76(3):228-38.
110. Maletkovic J, Dabbagh A, Zhang D, Zahid A, Bergsneider M, Wang MB, et al. Residual Tumor Confers a 10-Fold Increased Risk of Regrowth in Clinically Nonfunctioning Pituitary Tumors. *J Endocr Soc*. 2019;3(10):1931-41.
111. Chen Y, Wang CD, Su ZP, Chen YX, Cai L, Zhuge QC, et al. Natural history of postoperative nonfunctioning pituitary adenomas: a systematic review and meta-analysis. *Neuroendocrinology*. 2012;96(4):333-42.
112. Turner HE, Stratton IM, Byrne JV, Adams CB, Wass JA. Audit of selected patients with nonfunctioning pituitary adenomas treated without irradiation - a follow-up study. *Clin Endocrinol (Oxf)*. 1999;51(3):281-4.

113. Woollons AC, Hunn MK, Rajapakse YR, Toomath R, Hamilton DA, Conaglen JV, et al. Non-functioning pituitary adenomas: indications for postoperative radiotherapy. *Clin Endocrinol (Oxf)*. 2000;53(6):713-7.
114. Soto-Ares G, Cortet-Rudelli C, Assaker R, Boulinguez A, Dubest C, Dewailly D, et al. MRI protocol technique in the optimal therapeutic strategy of non-functioning pituitary adenomas. *Eur J Endocrinol*. 2002;146(2):179-86.
115. Greenman Y, Ouaknine G, Veshchev I, Reider G, II, Segev Y, Stern N. Postoperative surveillance of clinically nonfunctioning pituitary macroadenomas: markers of tumour quiescence and regrowth. *Clin Endocrinol (Oxf)*. 2003;58(6):763-9.
116. Dekkers OM, Pereira AM, Roelfsema F, Voormolen JH, Neelis KJ, Schroijen MA, et al. Observation alone after transsphenoidal surgery for nonfunctioning pituitary macroadenoma. *J Clin Endocrinol Metab*. 2006;91(5):1796-801.
117. van den Bergh AC, van den Berg G, Schoorl MA, Sluiter WJ, van der Vliet AM, Hoving EW, et al. Immediate postoperative radiotherapy in residual nonfunctioning pituitary adenoma: beneficial effect on local control without additional negative impact on pituitary function and life expectancy. *Int J Radiat Oncol Biol Phys*. 2007;67(3):863-9.
118. Losa M, Mortini P, Barzaghi R, Ribotto P, Terreni MR, Marzoli SB, et al. Early results of surgery in patients with nonfunctioning pituitary adenoma and analysis of the risk of tumor recurrence. *J Neurosurg*. 2008;108(3):525-32.
119. O'Sullivan EP, Woods C, Glynn N, Behan LA, Crowley R, O'Kelly P, et al. The natural history of surgically treated but radiotherapy-naive nonfunctioning pituitary adenomas. *Clin Endocrinol (Oxf)*. 2009;71(5):709-14.

120. Reddy R, Cudlip S, Byrne JV, Karavitaki N, Wass JA. Can we ever stop imaging in surgically treated and radiotherapy-naive patients with non-functioning pituitary adenoma? *Eur J Endocrinol*. 2011;165(5):739-44.
121. Karamouzis I, Berardelli R, Prencipe N, Berton A, Bona C, Stura G, et al. Retrospective observational analysis of non-irradiated non-functioning pituitary adenomas. *J Endocrinol Invest*. 2015;38(11):1191-7.
122. Vargas G, Gonzalez B, Ramirez C, Ferreira A, Espinosa E, Mendoza V, et al. Clinical characteristics and treatment outcome of 485 patients with nonfunctioning pituitary macroadenomas. *Int J Endocrinol*. 2015;2015:756069.
123. Raverot G, Dantony E, Beauvy J, Vasiljevic A, Mikolasek S, Borson-Chazot F, et al. Risk of Recurrence in Pituitary Neuroendocrine Tumors: A Prospective Study Using a Five-Tiered Classification. *J Clin Endocrinol Metab*. 2017;102(9):3368-74.
124. Raverot G, Vasiljevic A, Jouanneau E. Prognostic factors of regrowth in nonfunctioning pituitary tumors. *Pituitary*. 2018;21(2):176-82.
125. Micko AS, Wohrer A, Wolfsberger S, Knosp E. Invasion of the cavernous sinus space in pituitary adenomas: endoscopic verification and its correlation with an MRI-based classification. *J Neurosurg*. 2015;122(4):803-11.
126. Langlois F, Lim DST, Yedinak CG, Cetas I, McCartney S, Cetas J, et al. Predictors of silent corticotroph adenoma recurrence; a large retrospective single center study and systematic literature review. *Pituitary*. 2018;21(1):32-40.
127. Galm BP, Martinez-Salazar EL, Swearingen B, Torriani M, Klibanski A, Bredella MA, et al. MRI texture analysis as a predictor of tumor recurrence or progression in patients with clinically non-functioning pituitary adenomas. *Eur J Endocrinol*. 2018;179(3):191-8.

128. Ramirez C, Cheng S, Vargas G, Asa SL, Ezzat S, Gonzalez B, 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(5):1745-51.
129. Righi A, Agati P, Sisto A, Frank G, Faustini-Fustini M, Agati R, et al. A classification tree approach for pituitary adenomas. *Hum Pathol.* 2012;43(10):1627-37.
130. Hallen T, Olsson DS, Hammarstrand C, Orndal C, Engvall A, Ragnarsson O, et al. MCM7 as a marker of postsurgical progression in non-functioning pituitary adenomas. *Eur J Endocrinol.* 2021;184(4):521-31.
131. Falch CM, Sundaram AYM, Oystese KA, Normann KR, Lekva T, Silamikelis I, et al. Gene expression profiling of fast- and slow-growing non-functioning gonadotroph pituitary adenomas. *Eur J Endocrinol.* 2018;178(3):295-307.
132. Brada M, Rajan B, Traish D, Ashley S, Holmes-Sellors PJ, Nussey S, et al. The long-term efficacy of conservative surgery and radiotherapy in the control of pituitary adenomas. *Clin Endocrinol (Oxf).* 1993;38(6):571-8.
133. Tampourlou M, Ntali G, Ahmed S, Arlt W, Ayuk J, Byrne JV, et al. Outcome of Nonfunctioning Pituitary Adenomas That Regrow After Primary Treatment: A Study From Two Large UK Centers. *J Clin Endocrinol Metab.* 2017;102(6):1889-97.
134. Chanson P, Dormoy A, Dekkers OM. Use of radiotherapy after pituitary surgery for non-functioning pituitary adenomas. *Eur J Endocrinol.* 2019;181(1):D1-D13.
135. Gittoes NJL, Bates AS, Tse W, Bullivan B, Sheppard MC, Clayton RN, et al. Radiotherapy for non-functioning pituitary tumours. *Clin Endocrinol (Oxf).* 1998;48:331-7.

136. Jaffrain-Rea ML, Derome P, Bataini JP, Thomopoulos P, Bertagna X, Luton JP. Influence of radiotherapy on long-term relapse in clinically non-secreting pituitary adenomas. A retrospective study (1970-1988). *Eur J Med.* 1993;2(7):398-403.
137. Olsson DS, Buchfelder M, Schlaffer S, Bengtsson BA, Jakobsson KE, Johannsson G, et al. Comparing progression of non-functioning pituitary adenomas in hypopituitarism patients with and without long-term GH replacement therapy. *Eur J Endocrinol.* 2009;161(5):663-9.
138. Park P, Chandler WF, Barkan AL, Orrego JJ, Cowan JA, Griffith KA, et al. The role of radiation therapy after surgical resection of nonfunctional pituitary macroadenomas. *Neurosurgery.* 2004;55(1):100-6; discussion 6-7.
139. Tsang RW, Brierley JD, Panzarella T, Gospodarowicz MK, Sutcliffe SB, Simpson WJ. Radiation therapy for pituitary adenoma: treatment outcome and prognostic factors. *Int J Radiat Oncol Biol Phys.* 1994;30(3):557-65.
140. Minniti G, Scaringi C, Poggi M, Jaffrain Rea ML, Trillo G, Esposito V, et al. Fractionated stereotactic radiotherapy for large and invasive non-functioning pituitary adenomas: long-term clinical outcomes and volumetric MRI assessment of tumor response. *Eur J Endocrinol.* 2015;172(4):433-41.
141. Milker-Zabel S, Debus J, Thilmann C, Schlegel W, Wannemacher M. Fractionated stereotactically guided radiotherapy and radiosurgery in the treatment of functional and nonfunctional adenomas of the pituitary gland. *Int J Radiat Oncol Biol Phys.* 2001;50(5):1279-86.
142. Paek SH, Downes MB, Bednarz G, Keane WM, Werner-Wasik M, Curran WJ, Jr., et al. Integration of surgery with fractionated stereotactic radiotherapy for treatment of nonfunctioning pituitary macroadenomas. *Int J Radiat Oncol Biol Phys.* 2005;61(3):795-808.

143. Colin P, Jovenin N, Delemer B, Caron J, Grulet H, Hecart AC, et al. Treatment of pituitary adenomas by fractionated stereotactic radiotherapy: a prospective study of 110 patients. *Int J Radiat Oncol Biol Phys.* 2005;62(2):333-41.
144. Minniti G, Traish D, Ashley S, Gonsalves A, Brada M. Fractionated stereotactic conformal radiotherapy for secreting and nonsecreting pituitary adenomas. *Clin Endocrinol (Oxf).* 2006;64(5):542-8.
145. Schalin-Jantti C, Valanne L, Tenhunen M, Setälä K, Paetau A, Sane T, et al. Outcome of fractionated stereotactic radiotherapy in patients with pituitary adenomas resistant to conventional treatments: a 5.25-year follow-up study. *Clin Endocrinol (Oxf).* 2010;73(1):72-7.
146. Astradsson A, Wiencke AK, Munck af Rosenschold P, Engelholm SA, Ohlhues L, Roed H, et al. Visual outcome after fractionated stereotactic radiation therapy of benign anterior skull base tumors. *J Neurooncol.* 2014;118(1):101-8.
147. Bostrom JP, Meyer A, Pintea B, Gerlach R, Surber G, Lammering G, et al. Risk-adapted single or fractionated stereotactic high-precision radiotherapy in a pooled series of nonfunctioning pituitary adenomas: high local control and low toxicity. *Strahlenther Onkol.* 2014;190(12):1095-103.
148. Bir SC, Murray RD, Ambekar S, Bollam P, Nanda A. Clinical and Radiologic Outcome of Gamma Knife Radiosurgery on Nonfunctioning Pituitary Adenomas. *J Neurol Surg B Skull Base.* 2015;76(5):351-7.
149. Hoybye C, Rahn T. Adjuvant Gamma Knife radiosurgery in non-functioning pituitary adenomas; low risk of long-term complications in selected patients. *Pituitary.* 2009;12(3):211-6.

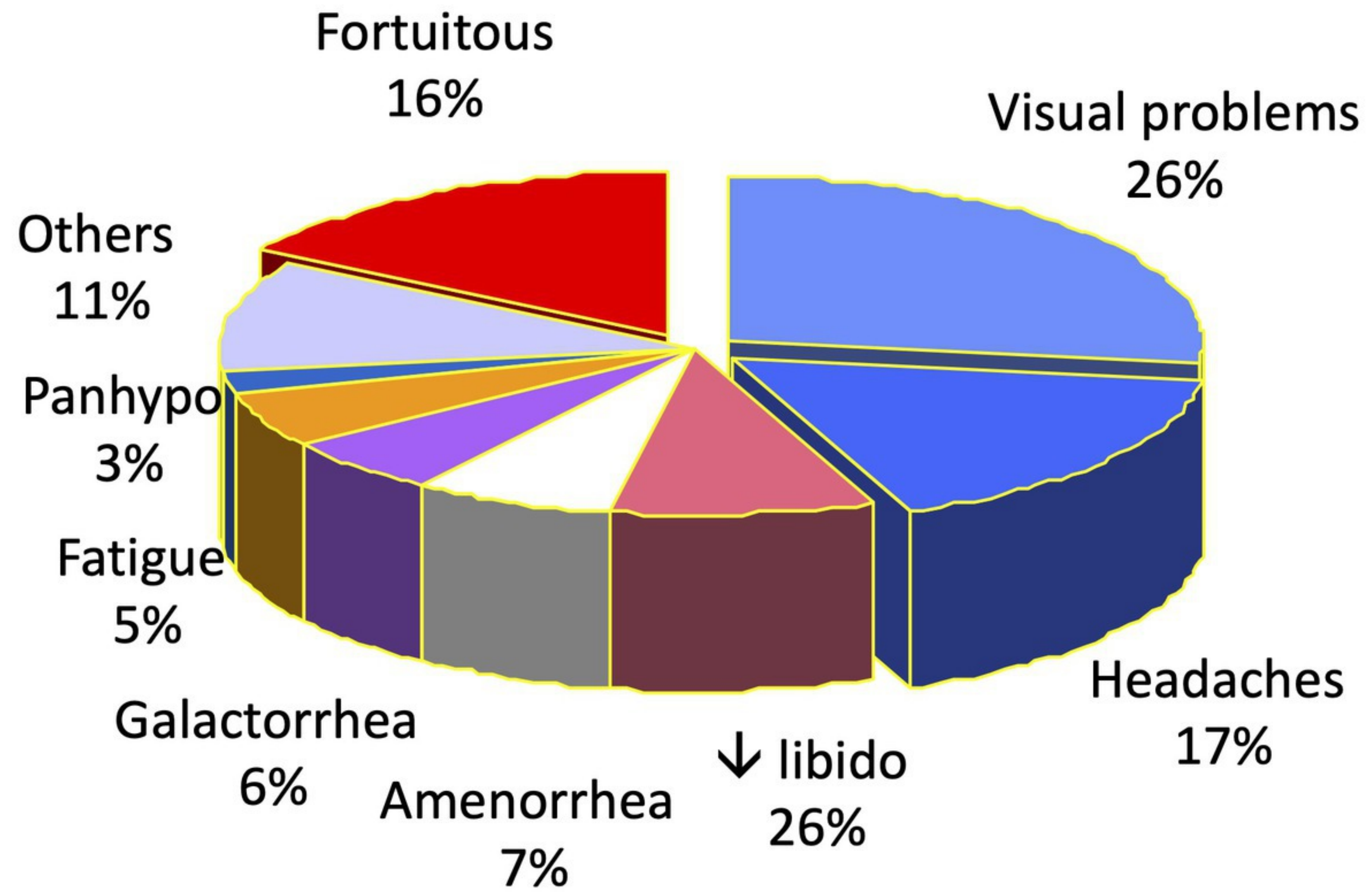
150. Iwai Y, Yamanaka K, Yoshioka K, Yoshimura M, Honda Y, Matsusaka Y, et al. [The usefulness of adjuvant therapy using gamma knife radiosurgery for the recurrent or residual nonfunctioning pituitary adenomas]. *No Shinkei Geka*. 2005;33(8):777-83.
151. Lee CC, Kano H, Yang HC, Xu Z, Yen CP, Chung WY, et al. Initial Gamma Knife radiosurgery for nonfunctioning pituitary adenomas. *J Neurosurg*. 2014;120(3):647-54.
152. Liscak R, Vladyka V, Marek J, Simonova G, Vymazal J. Gamma knife radiosurgery for endocrine-inactive pituitary adenomas. *Acta Neurochir (Wien)*. 2007;149(10):999-1006; discussion
153. Losa M, Picozzi P, Motta M, Valle M, Franzin A, Mortini P. The role of radiation therapy in the management of non-functioning pituitary adenomas. *J Endocrinol Invest*. 2011;34(8):623-9.
154. Losa M, Spatola G, Albano L, Gandolfi A, Del Vecchio A, Bolognesi A, et al. Frequency, pattern, and outcome of recurrences after gamma knife radiosurgery for pituitary adenomas. *Endocrine*. 2016.
155. Mingione V, Yen CP, Vance ML, Steiner M, Sheehan J, Laws ER, et al. Gamma surgery in the treatment of nonsecretory pituitary macroadenoma. *J Neurosurg*. 2006;104(6):876-83.
156. Petrovich Z, Yu C, Giannotta SL, Zee CS, Apuzzo ML. Gamma knife radiosurgery for pituitary adenoma: early results. *Neurosurgery*. 2003;53(1):51-9; discussion 9-61.
157. Picozzi P, Losa M, Mortini P, Valle MA, Franzin A, Attuati L, et al. Radiosurgery and the prevention of regrowth of incompletely removed nonfunctioning pituitary adenomas. *J Neurosurg*. 2005;102 Suppl:71-4.

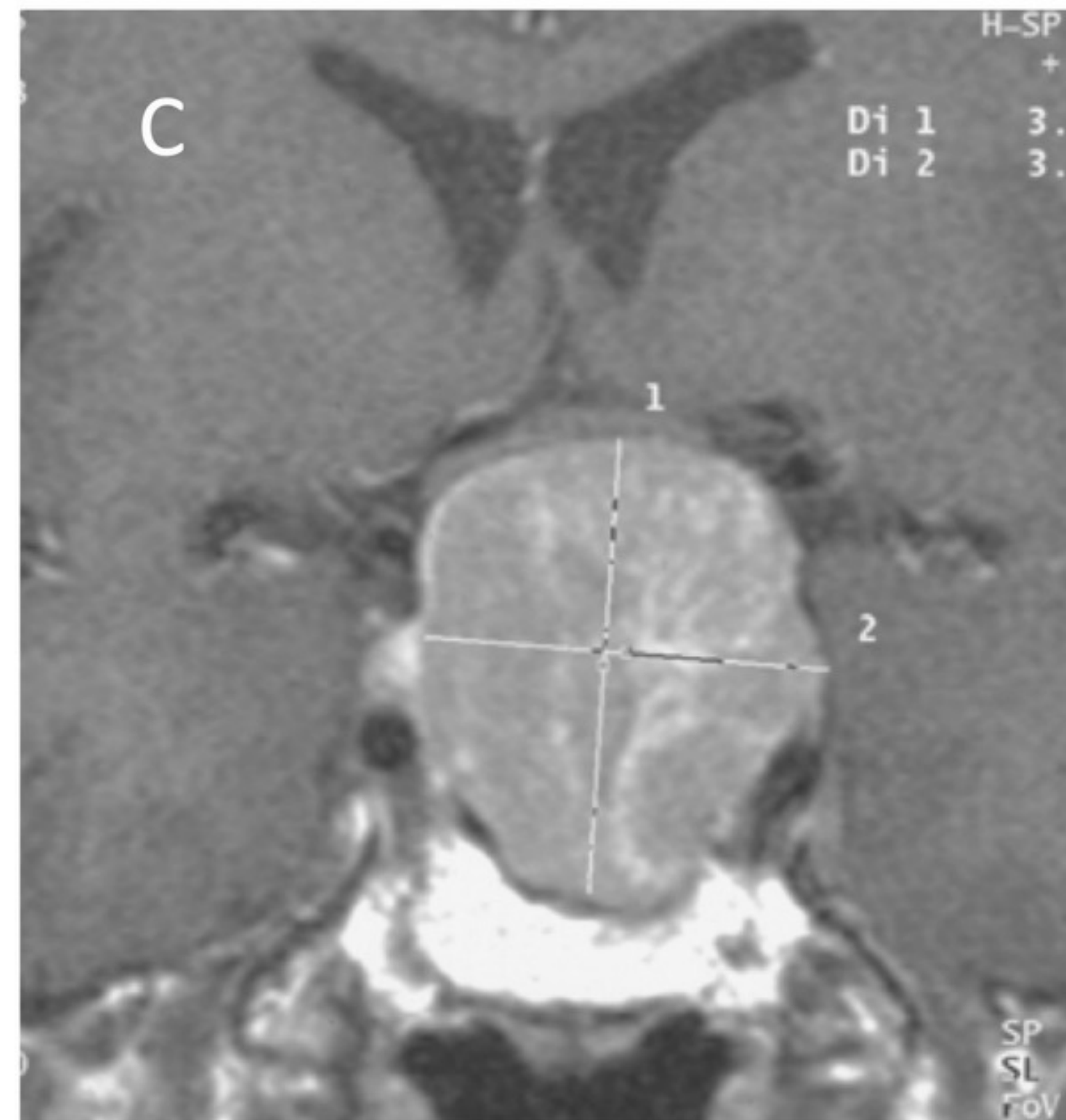
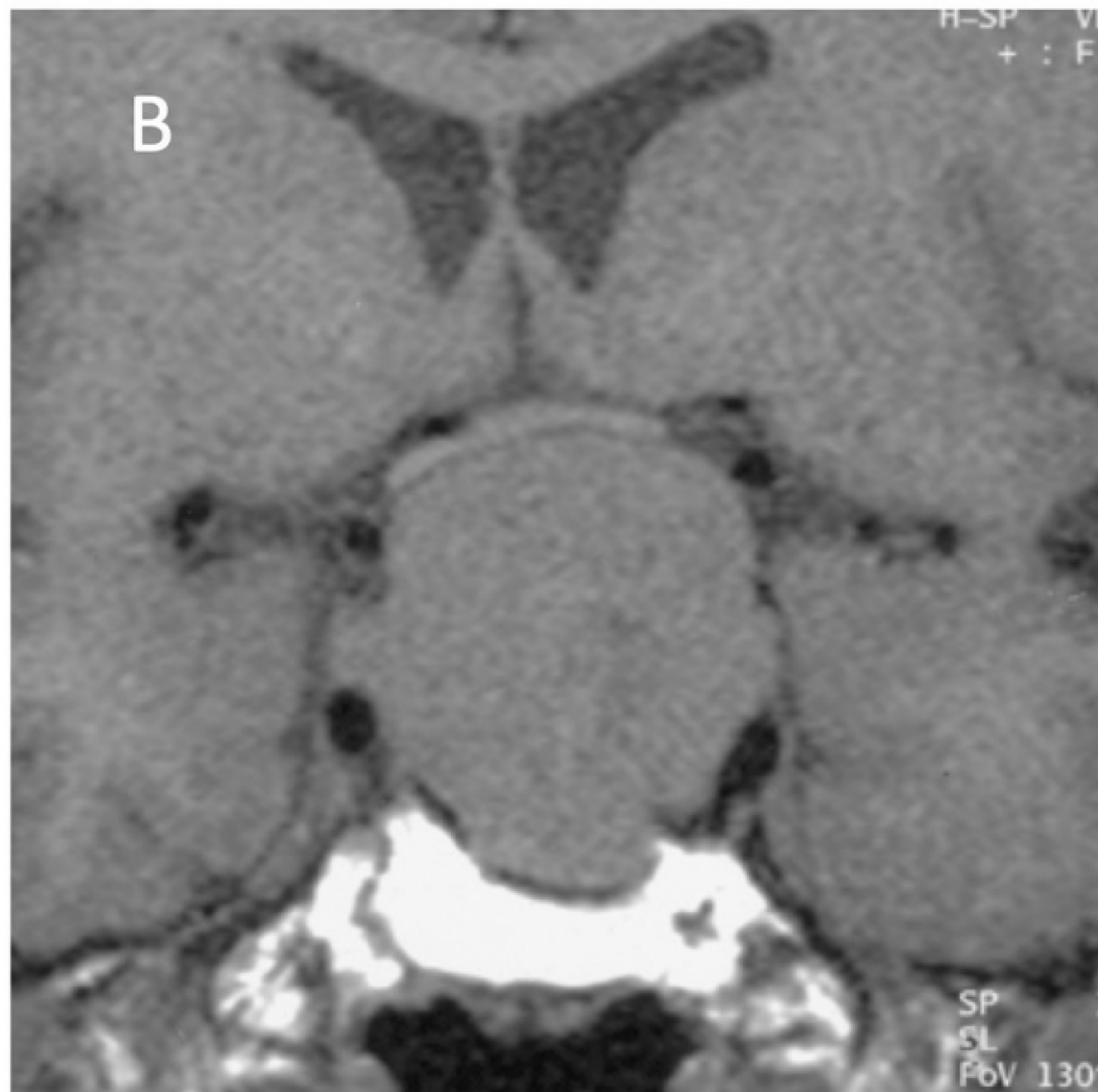
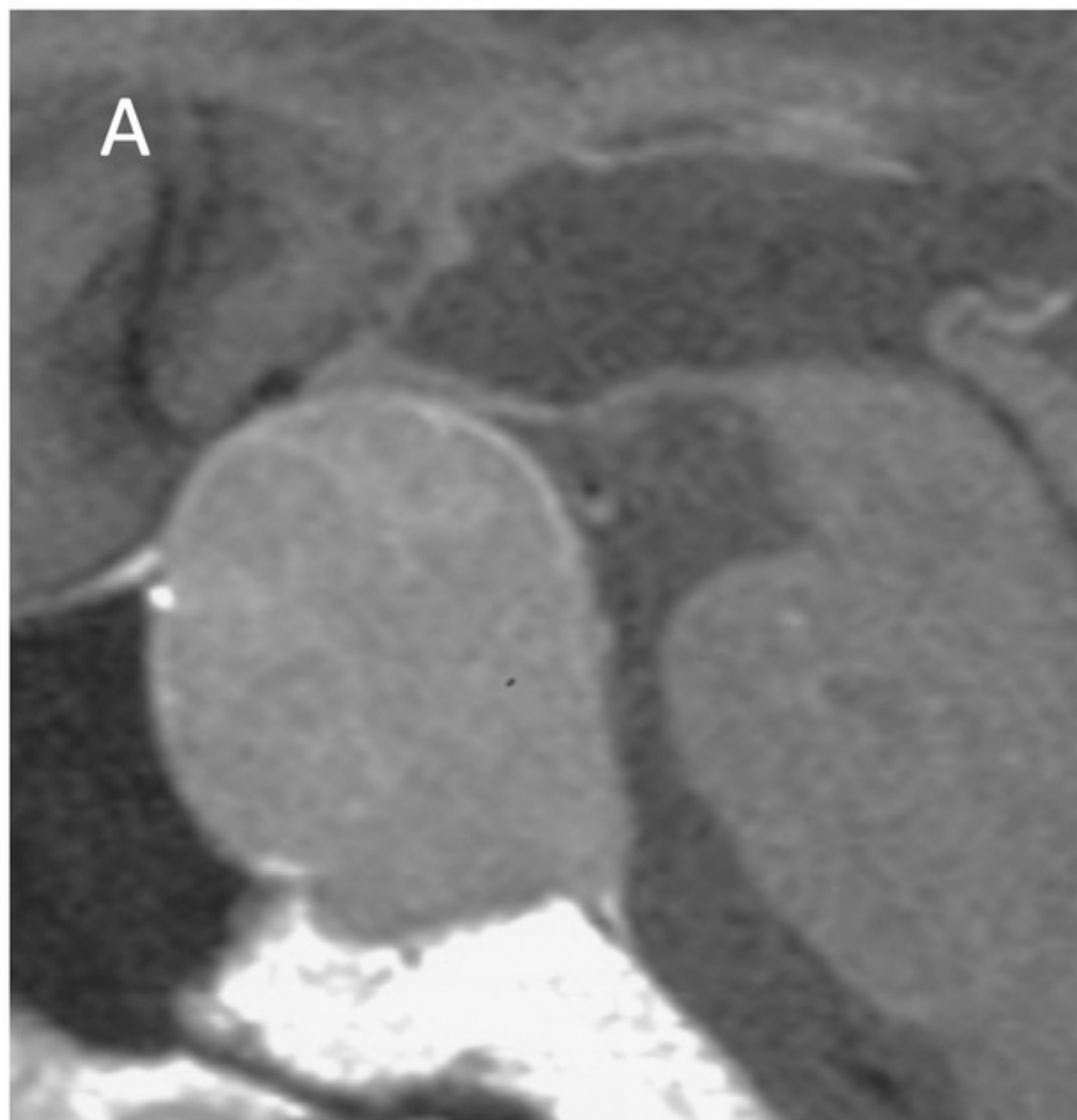
158. Pollock BE, Cochran J, Natt N, Brown PD, Erickson D, Link MJ, et al. Gamma knife radiosurgery for patients with nonfunctioning pituitary adenomas: results from a 15-year experience. *Int J Radiat Oncol Biol Phys.* 2008;70(5):1325-9.
159. Sheehan JP, Kondziolka D, Flickinger J, Lunsford LD. Radiosurgery for residual or recurrent nonfunctioning pituitary adenoma. *J Neurosurg.* 2002;97(5 Suppl):408-14.
160. Sheehan JP, Starke RM, Mathieu D, Young B, Sneed PK, Chiang VL, et al. Gamma Knife radiosurgery for the management of nonfunctioning pituitary adenomas: a multicenter study. *J Neurosurg.* 2013;119(2):446-56.
161. Wilson PJ, De-Loyde KJ, Williams JR, Smee RI. A single centre's experience of stereotactic radiosurgery and radiotherapy for non-functioning pituitary adenomas with the Linear Accelerator (Linac). *J Clin Neurosci.* 2012;19(3):370-4.
162. Wowra B, Stummer W. Efficacy of gamma knife radiosurgery for nonfunctioning pituitary adenomas: a quantitative follow up with magnetic resonance imaging-based volumetric analysis. *J Neurosurg.* 2002;97(5 Suppl):429-32.
163. Chen Y, Li ZF, Zhang FX, Li JX, Cai L, Zhuge QC, et al. Gamma knife surgery for patients with volumetric classification of nonfunctioning pituitary adenomas: a systematic review and meta-analysis. *Eur J Endocrinol.* 2013;169(4):487-95.
164. Erridge SC, Conkey DS, Stockton D, Strachan MW, Statham PF, Whittle IR, et al. Radiotherapy for pituitary adenomas: long-term efficacy and toxicity. *Radiother Oncol.* 2009;93(3):597-601.
165. Minniti G, Traish D, Ashley S, Gonsalves A, Brada M. Risk of second brain tumor after conservative surgery and radiotherapy for pituitary adenoma: update after an additional 10 years. *J Clin Endocrinol Metab.* 2005;90(2):800-4.

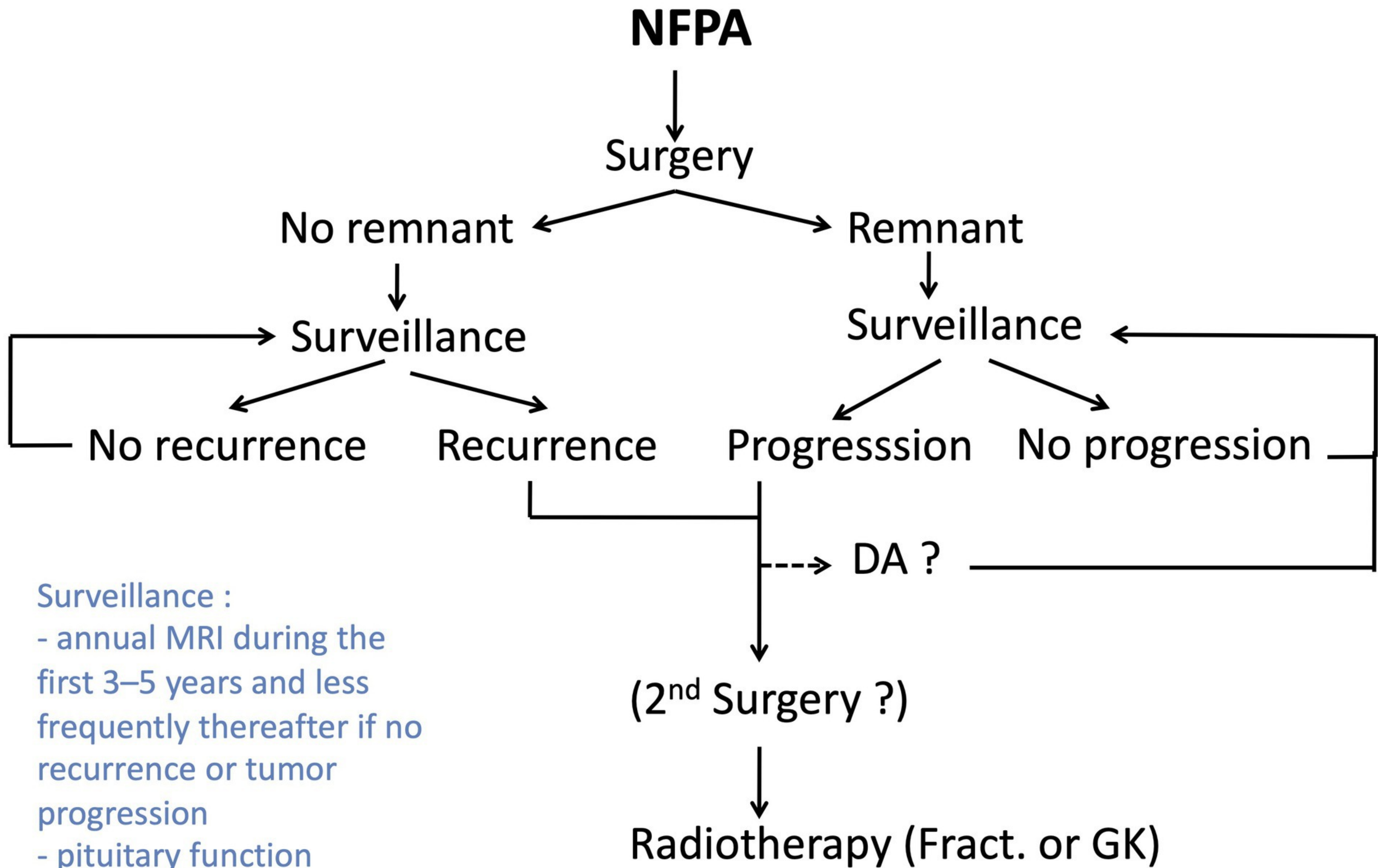
166. Brada M, Ashley S, Ford D, Traish D, Burchell L, Rajan B. Cerebrovascular mortality in patients with pituitary adenoma. *Clin Endocrinol (Oxf)*. 2002;57(6):713-7.
167. Brada M, Burchell L, Ashley S, Traish D. The incidence of cerebrovascular accidents in patients with pituitary adenoma. *Int J Radiat Oncol Biol Phys*. 1999;45(3):693-8.
168. Sherlock M, Ayuk J, Tomlinson JW, Toogood AA, Aragon-Alonso A, Sheppard MC, et al. Mortality in patients with pituitary disease. *Endocr Rev*. 2010;31(3):301-42.
169. Plummer C, Henderson RD, O'Sullivan JD, Read SJ. Ischemic stroke and transient ischemic attack after head and neck radiotherapy: a review. *Stroke*. 2011;42(9):2410-8.
170. Yavropoulou MP, Tsoli M, Barkas K, Kaltsas G, Grossman A. The natural history and treatment of non-functioning pituitary adenomas (non-functioning PitNETs). *Endocr Relat Cancer*. 2020;27(10):R375-R90.
171. Greenman Y, Bronstein MD. Cabergoline should be attempted in progressing non-functioning pituitary macroadenoma. *Eur J Endocrinol*. 2021;185(4):D11-D20.
172. Greenman Y, Tordjman K, Osher E, Veshchev I, Shenkerman G, Reider G, II, et al. Postoperative treatment of clinically nonfunctioning pituitary adenomas with dopamine agonists decreases tumour remnant growth. *Clin Endocrinol (Oxf)*. 2005;63(1):39-44.
173. Greenman Y, Cooper O, Yaish I, Robenshtok E, Sagiv N, Jonas-Kimchi T, et al. Treatment of clinically nonfunctioning pituitary adenomas with dopamine agonists. *Eur J Endocrinol*. 2016;175(1):63-72.
174. Batista RL, Musolino NRC, Cescato VAS, da Silva GO, Medeiros RSS, Herkenhoff CGB, et al. Cabergoline in the management of residual nonfunctioning

pituitary adenoma: A single-center, open-label, 2-year randomized clinical trial. *Am J Clin Oncol.* 2019;42(2):221-7.

175. Colao A, Di Somma C, Pivonello R, Faggiano A, Lombardi G, Savastano S. Medical therapy for clinically non-functioning pituitary adenomas. *Endocr Relat Cancer.* 2008;15(4):905-15.







Surveillance :

- annual MRI during the first 3–5 years and less frequently thereafter if no recurrence or tumor progression
- pituitary function