Surgical Indications and Results for Non-functioning Pituitary Adenomas

a report by

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Non-functioning pituitary adenomas (NFPAs) are benign tumors that do not produce any biologically active hormones and constitute 16–20% of all pituitary adenomas.[1] NFPAs have a similar clinical presentation, but represent a heterogeneous group of tumors. Recent advances in immuno-cytochemical and molecular biological techniques showed that more than 80% of clinical NFPAs, previously called chromophobe adenomas, contain follicle-stimulating hormone (FSH), luteinizing hormone (LH), the common alpha-subunit, FSH beta-subunit, or LH beta-subunit.[2,3] NFPAs may, rarely, stain positive for adrenocorticotropic hormone (ACTH), prolactin (PRL), thyroid-stimulating hormone (TSH), or growth hormone (GH) without any clinical or biochemical evidence of hormone hypersecretion.[4,5]

NFPAs are usually asymptomatic until they become large enough to cause mass effects. Diagnosis is frequently made when they are at the macro-adenoma stage. Visual deficit is the most frequent symptom that leads a patient to discover a pituitary mass. Patients often show bi-temporal hemianopsia secondary to compression of the optic chiasm by suprasellar extension of the tumor. If the lesion invades the cavernous sinus, it can also compromise oculomotor nerves, causing diplopia, ptosis, and ophthalmoplegia. Another common symptom is headache, which is present in 20–50% of cases.[6–9] Patients may report hormonal abnormalities, most commonly hypogonadism (decreased libido, impotence, or menstrual dysfunction in pre-menopausal women), which may be secondary to hyperprolactinemia. Other pituitary deficiencies may be present in more than 30% of patients with macro-adenomas.[9] An uncommon presentation of NFPAs is tumor apoplexy due to sudden bleeding within the adenomatous tissue. Patients develop a sudden and excruciating headache, often accompanied by nausea and vomiting. Within hours, neurological deficits, secondary to compression of the optic pathway or oculomotor nerves, ensue. While most cases of pituitary apoplexy are spontaneous, precipitating factors may include head injury, anticoagulant therapy, radiation therapy, or dynamic endocrine tests.[10]

Pituitary Incidentalomas—Indications for Treatment

An increasing proportion of NFPAs are currently recognized by chance when brain imaging (magnetic resonance imaging [MRI] or computed tomography [CT]) is performed for unrelated reasons (the so-called 'pituitary incidentalomas').[1,11] While there is a current consensus that NFPAs that are causing symptoms should be treated to allow decompression of the normal pituitary gland and the optic pathway, there is debate as to whether pituitary incidentalomas require treatment when first detected.

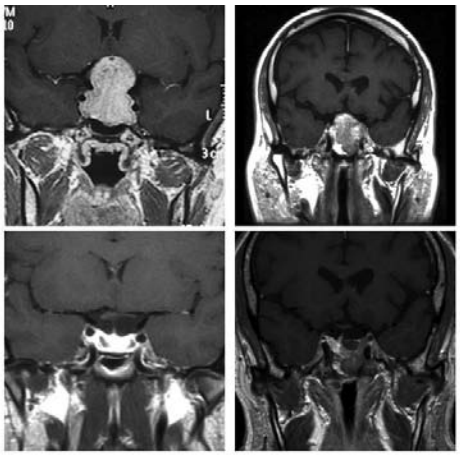
NFPAs that present as incidentalomas can occur as either micro- or macro-adenomas. This distinction is important, as there are practical differences in the management of these two tumors.[11] Incidental micro-adenomas do not cause symptoms related to mass effect and, once hormonal hypersecretion has been excluded, they should be managed conservatively.[1,12] Observation with close imaging monitoring of tumor size is recommended with MRI and basal hormone testing at six and 12 months.[13] If tumor size remains stable and the pituitary function is not compromised, the patient can be followed up less frequently (e.g. every two years).[11] Growth of micro-adenomas is usually slow. Prospective studies on the natural history of these tumors demonstrated that significant growth over time was relatively uncommon.[1,12,14] In a Japanese survey, fewer than 10% of micro-adenomas increased in size during a median follow-up of 45 months.[15] Whenever significant changes in tumor size or alterations of pituitary function are detected, surgery is advised to prevent hypopituitarism or visual deficit.[12] When incidentalomas are discovered at a later stage (i.e. when they are macro-adenomas), there is much controversy about the indications for treatment. At this stage of development, the natural history of the lesion is characterized by a trend for slow growth.[14] Several factors must be taken into account when deciding which patients should be referred for therapy and which to closely monitor. Large tumors and a young age should favor the decision to treat the patient, while co-existent comorbidity may suggest a more conservative approach.

Surgical Treatment

The first-choice treatment for NFPAs is surgery and should be performed by a surgeon experienced in pituitary surgery. The goals of surgical treatment are to remove as much tumor as possible, relieve compression on adjacent nervous structures, and obtain a definitive pathological diagnosis. Usually a trans-sphenoidal approach is used. With tumors that have a prevalent extension well beyond the boundaries of the sella, a transcranial surgical approach is indicated.[16] Disadvantages of the transcranial approach include the risk for mortality, due to damage to vital structures, major morbidity (risk for seizures, worsening of vision, increased duration of hospitalization), hypopituitarism, and diabetes insipidus. The trans-sphenoidal technique, via sub-labial or intranasal incision, is preferred in the vast majority of patients (>95%).

The natural course of NFPAs is largely unknown; if the tumor is large, the risk for further expansion is expected to be high, since the tumor has a proven propensity to grow. At present, only a few studies have assessed the natural course of untreated NFPAs, mainly because the majority of patients with macro-adenomas are operated on. Some recent studies have suggested a higher propensity for growth than previously thought. Karavitaki et al.[17] studied 24 patients who had NFPAs and found that the 48-month probability of enlargement was 44%. Of this group, 57% showed new or worsening visual-field defects and an additional 21% showed chiasmatic compression on imaging, without vision deterioration. Arita and colleagues[18] found that 21 of

Figure 1: Coronal Pre-operative (top) and Post-operative (bottom) Gadolinium-enhanced, T_1-weighted Magnetic Resonance Images of Two Patients Undergoing Surgery Because of Non-functioning Pituitary Adenomas



In the first patient (left lower panel), no apparent residual tumor is visible three months after surgery. Further imaging follow-up showed no tumor recurrence 30 months after surgery. In the second patient (right lower panel), there is evidence of a tumor near the left cavernous sinus. This patient underwent gamma-knife radio-surgery three months afterwards. At the last follow-up, one year after gamma knife surgery, the tumor was unchanged.

Table 1: Frequency of Residual Tumor Visible on the First Post-operative Neuro-imaging in Patients Operated on Because of a Non-functioning Pituitary Adenoma in Recently Published Surgical Series

Authors	Year	Number of Patients	Number with Residual Post-op. Tumor (%)	Type of Imaging
Zhang et al.[36]	1999	208	62 (29.8%)	CT–MRI
Woollons et al.[33]	2000	72	52 (72.2%)	CT–MRI
Greenman et al.[35]	2003	122	92 (75.4%)	MRI
Nomikos et al.[29]	2004	721	278 (38.6%)	CT–MRI
Dekkers et al.[19]	2006	109	80 (73.0%)	MRI
Ferrante et al.[8]	2006	290	185 (64.5%)	CT–MRI
Losa et al.[9]	2008	475	173 (36.4%)	MRI

CT = computed tomography; MRI = magnetic resonance imaging.

42 (50%) NFPAs (mean size 18.3±7mm) increased by at least 10% over an average of 32 months after the initial evaluation. Ten patients became symptomatic over a mean of about five years, with four of these 10 (9.5% of the entire cohort) suffering symptomatic pituitary apoplexy.

Early Results of Surgery

Peri-operative mortality is usually minimal—fewer than 1% of cases—when performed by an experienced surgeon.[9,19] The most frequent early complication of surgery is diabetes insipidus, which is usually transient. Other complications include cerebrospinal leakage (seldom requiring surgical repair), transient hyponatremia, visual worsening or transient cranial nerve palsy, and sellar hematoma.[9]

Resolution of clinical symptoms has been reported in various surgical series. Trans-sphenoidal surgery allows improvement of visual disturbances in approximately 80% of all patients.[16,20] Visual recovery may be demonstrated a few days after surgery.[21–23] In a recent study by Losa and co-workers, visual function normalized in 110 (39.4%) and improved in 141 (50.6%) of the 279 patients with pre-operative impairment of visual function.[9] Resolution of oculomotor nerve palsy occurred in 18 of the 22 patients (81.8%) with diplopia at presentation.[9] Surgery provides immediate relief of headache in the majority of patients complaining of this symptom at diagnosis.[16,24,25]

Surgical treatment improves neurological alterations in the majority of patients with NFPAs. Recovery of impaired pituary function is, in contrast, less likely. In the literature there is large variability in the results concerning pituitary function after surgery. In a recent review by Dekkers et al.,[26] some studies showed, to a variable degree, an improvement after surgery,[6,23,27–29] whereas others could not demonstrate significant improvement in pituitary function[7,30] or even reported worsening of pituitary function.[19,31,32] It is likely that some of the variability in the results might be explained by the different criteria used to define hypopituitarism, the use of post-operative radiation therapy, and differences of patient baseline characteristics.[16] Dekkers reported that hypopituitarism is still present in a considerable proportion of patients after surgery (GH deficiency in about 83%, gonadotropin deficiency in about 60%, and TSH and ACTH deficiency in about 30%).[26] In our series of 482 patients, post-operative worsening of gonadal, thyroid, or adrenal function occurred in 5.8, 5.6, and 7.5% of patients with normal gonadal, thyroid, or adrenal function before surgery, respectively.[9] Recovery of normal gonadal, thyroid, or adrenal function occurred in 32.8, 35.7, and 41.6% of the patients with impaired gonadal, thyroid, or adrenal function before surgery, respectively.[9] As a whole, 49.0, 20.3, and 19.6% of the patients had impaired gonadal, thyroid, and adrenal function after surgery, respectively.[9]

Improvement of clinical symptoms by no means indicates total removal of the tumor.[16] Due to the lack of a reliable tumor markers, the best method to assess the degree of surgical de-bulking is to obtain an imaging study (MRI is preferable to CT) three to six months after surgery (see *Figure 1*). As most NFPAs are large and invasive at diagnosis, persistence of residual tumor after surgery is relatively frequent (see *Table 1*). In an Italian database of NFPAs, surgery represented the first therapeutic approach (98% of patients), and radiological cure, defined as the absence of tumor remnants on post-operative neuro-imaging, was achieved in 35.5% of patients.[8] This result is in agreement with previous studies.[33–35] In centers that are highly specialized in pituitary surgery and perform high volumes of surgical procedures each year, the reported percentage of apparent total tumor removal approaches 60–70% of patients with NFPAs.[9,29,36] The variables that are associated with an unfavorable early surgical result are the presence of tumor invasion into the cavernous sinus,[9,35] greater maximum tumor diameter,[9,29] and, in our experience, absence of tumor apoplexy.[9]

Tumor Recurrence and Treatment After Surgery

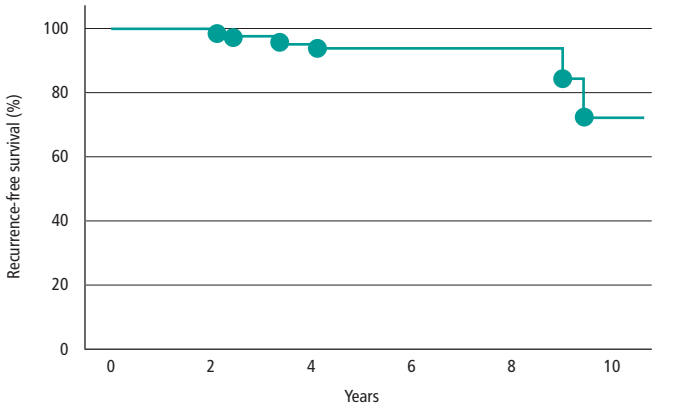
Clinical recurrence of NFPAs is defined by the occurrence of symptoms secondary to compression of the surrounding structures. By this definition, it is clear that clinical recurrence can be caused only when the tumor is very large, necessitating another surgical procedure to improve the clinical picture. In old surgical series, such recurrences were reported in more than 50% at five years.[37,38] A goal of therapy should be to avoid repeat surgery, if not strictly necessary. A more precise definition of tumor recurrence is based on imaging criteria, which needs to be performed routinely in patients operated on for NFPAs. Recurrence of the pituitary tumor is defined by the appearance on repeated MRI of pathological tissue not detected at an earlier examination or by further growth of adenomatous tissue that was always detected on previous MRIs.

Recurrence of NFPAs after surgery is reported in between 12 and 45% of cases.[7,16,24,33,39–41] This variability reflects different surgical expertise, different criteria to define recurrence, the length of follow-up, and the use of adjuvant radiotherapy.[16] In some studies the completeness of tumor removal was not objectively ascertained. Recurrence after apparent complete tumor removal seems to be uncommon. In a small series,[42] only two of 32 patients (6.2%) with apparent gross total tumor removal and no post-operative radiotherapy had radiological recurrence of NFPAs after a mean follow-up of more than five years. Other studies also found a similarly low rate of tumor recurrence when the first post-operative MRI showed no residual tumor.[19,32,33,35] In our large series, the five-year recurrence-free survival of such patients was 87.1%.[9] The use of prophylactic radiation therapy may not be warranted, provided that patients are willing to continue a tight follow-up with appropriate imaging studies.

The risk for tumor re-growth in patients who have had an incomplete removal of an NFPA is more controversial. Most series[8,9,33,35,41] report a high risk for re-growth when the tumor residue is left untreated. In our series, the five-year recurrence-free survival was only 39.2% and the risk does not seem to plateau even after this interval.[9] In a study by Greenman and co-workers,[35] factors associated with a higher risk for tumor growth were tumor size and invasion before surgery and the size of the tumor residue after surgery. In contrast, our multivariate analysis failed to identify prognostic factors for the risk for tumor growth.[9]

Although not universally accepted, radiation therapy is considered a very effective adjuvant therapy after incomplete removal of NFPAs. There are no prospective trials that compare the effects of radiation versus observation alone, but several studies suggest a higher control of local growth with radiotherapy. In one study, 15-year recurrence-free survival was 93% in one institution that routinely administered radiotherapy to all patients operated on for NFPAs, compared with 33% in another institution that simply followed patients after surgery.[40] Multivariate analysis showed that the only prognostic factor for tumor re-growth was the administration of radiotherapy. A similar conclusion was reached in our recent series.[9] A highly significant difference in the likelihood of tumor recurrence between irradiated and non-irradiated patients with residual NFPAs after surgery has been confirmed in several other studies.[7,33,41,43] Similar control of local tumor growth can be achieved even with gamma-knife radio-surgery, which has the possible advantage of sparing the pituitary gland.[44] A recent update of our series of patients treated with the gamma-knife for residual NFPAs confirms our previous results (see *Figure 2*).

Figure 2: Kaplan-Meier Analysis of Time to Recurrence of Non-functioning Pituitary Adenoma in 135 Patients Who Had Residual or Recurring Tumor Treated with Gamma Knife Radio-surgery



Six patients had relapse during follow-up. In all six cases, there was growth of adenomatous tissue located in the contralateral side of the treated lesion. The recurrence-free survival at five years was 94.1% (95% confidence interval 88.3–99.9%).

Other studies report diverging results. Dekkers et al. reported tumor re-growth in only 10% of patients with residual NFPAs who did not undergo radiotherapy, with a mean time to tumor re-growth of approximately six years.[19]

Conclusion

NFPAs are the most frequent type of pituitary tumor necessitating surgical treatment. With the exception of small asymptomatic lesions discovered incidentally, or patients of advanced age in a poor health condition, patients with NFPAs should always undergo surgical removal of the pituitary tumor by an experienced neurosurgeon. Whenever possible, the less traumatic trans-sphenoidal approach should be used. Neurological symptoms due to compression of surrounding structures are expected to show clear improvement soon after surgery. Impaired pituitary function may recover in a small percentage of patients. Total removal of the tumor is the aim of surgery. This can be accomplished in about 50–70% of patients, but is unusual in patients with very large tumors that invade the cavernous sinus. If residual tumor is present after maximal surgical removal, the option is to irradiate the patient to diminish the likelihood of clinical recurrence of NFPA. This decision must be balanced against the possible risks of radiation. Even patients with apparent total removal of NFPAs must be monitored closely with neuroimaging to detect a possible early recurrence of the tumor so that an appropriate decision about further radiation therapy can be discussed with the patient. ■

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