

## CLINICAL STUDY

# Non-functioning pituitary adenoma database: a useful resource to improve the clinical management of pituitary tumors

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## Abstract

**Objective:** The long-term outcome of non-functioning pituitary adenoma (NFPA) patients is not clearly established, probably due to the low annual incidence and prolonged natural history of these rare tumors. The aim of this study was to evaluate clinical data at presentation and long-term post-surgery and radiotherapy outcome in a cohort of patients with NFPA.

**Design and methods:** A computerized database was developed using Access 2000 software (Microsoft Corporation, 1999). Retrospective registration of 295 NFPA patients was performed in seven Endocrinological Centers of North West Italy. Data were analyzed by STATA software.

**Results:** The main presenting symptoms were visual defects (67.8%) and headache (41.4%) and the most frequent pituitary deficit was hypogonadism (43.3%), since almost all tumors were macroadenomas (96.5%). Surgery was the first choice treatment (98% of patients) and total debulking was achieved in 35.5%. Radiotherapy was performed as adjuvant therapy after surgery in 41% of patients. At the follow-up, recurrence occurred in 19.2% of patients without post-surgical residual tumor after  $7.5 \pm 2.6$  years, regrowth in 58.4% of patients with post-surgical remnant after  $5.3 \pm 4.0$  years and residue enlargement in 18.4% of patients post-surgically treated with radiotherapy after  $8.1 \pm 7.3$  years.

**Conclusions:** Our database indicates that the goal of a definitive surgical cure has been achieved during the last decade in a low percentage of patients with NFPA. This tumor database may help to reduce the delay between symptom onset and diagnosis, to assess prognostic parameters for the follow-up of patients with different risk of recurrence and to define the efficacy and safety of different treatments and their association with mortality/morbidity.

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## Introduction

Non-functioning pituitary adenomas (NFPAs) are the most frequent type of pituitary tumors. Because of hormonal inactivity, patients bearing this tumor type often present with macroadenomas that cause neurological symptoms due to mass effects. Neurosurgery, by the transsphenoidal approach whenever possible, is the treatment of choice of NFPAs. However, given the frequent supra- or parasellar extension, surgical therapy is infrequently curative, leaving tumor remnants that regrow during long-term follow-up in a significant proportion of cases (1, 2). In this context, the use of post-operative radiotherapy is still controversial. Despite the demonstrated efficacy of radiotherapy in

preventing tumor regrowth (3, 4), the selection of patients who will benefit by this therapy is made difficult by the absence of specific markers of tumor aggressiveness along with the potential side effects of this procedure that include hypopituitarism, neurocognitive dysfunction and development of secondary intracranial tumor (2, 5, 6). As far as the medical therapy is concerned, the use of dopamine agonists and/or somatostatin analogs has been proposed, given the expression of both dopamine and somatostatin receptors in NFPAs (7–10). However, available data show that the efficacy of these agents as first choice treatment is negligible (11–15).

Since the long-term outcome of NFPA patients is not clearly established, probably due to the low annual

incidence and prolonged natural history of these rare tumors, we developed a computerized database to collect clinical, biochemical, radiological, ophthalmological, and outcome data of patients referred to seven Endocrinological Centers in North West Italy for diagnosis, cure and follow-up of NFPA. Results obtained from our database indicate that the goal of a definitive surgical cure has been only partially achieved in Italy during the last decade. These data should challenge endocrinologists and general practitioners to entertain early diagnosis of these insidious and slow-growing tumors.

## Materials and methods

### Patients

This retrospective registration took place between January 1 2004 and December 31 2004 in seven Endocrinological Centers of major teaching and general hospitals that represent highly qualified centers for diagnosis and treatment of pituitary tumors in the North-west Italian area. The protocol was approved by the local ethical committee of each hospital. Each medical record was relative to a patient with confirmed NFPA, diagnosed and followed in one of the participating centers subsequently to 1976. Clinical, biochemical, radiological, ophthalmological, and outcome data from 295 patients with NFPA were registered. Diagnosis of NFPA was based on the presence of a sellar lesion in the absence of hormonal hypersecretion and confirmed at histological examination of the surgically removed tissues. All patients performed computed tomography (CT) scan or magnetic resonance imaging (MRI). Immunohistochemical findings were available in a minority of tumors.

Tumor regrowth was investigated in 226 patients, after the exclusion of patients without a careful description of neuroradiological findings before and/or after therapeutical procedures, patients with radiological modifications occurred in concomitance with a change of imaging techniques and patients with a follow-up < 5 years ( $n=69$ ). On the basis of first post-operative imaging and the following therapeutical approach, patients were classified as follows: group A, patients with no neuroradiological evidence of residual tumor; group B, patients with post-operative tumor remnant who did not undergo radiation therapy; group C, patients with post-operative tumor remnant who were treated with radiotherapy after surgery.

### Non-functioning pituitary adenoma database

An evidence-based computerized pituitary tumor database was developed using Access 2000 software (Microsoft Corporation, 1999). The choice of specific fields was made to obtain a large and complete overview of patients with NFPA, including risk factors, associated diseases, signs and symptoms as well as hormonal,

neuroradiological, visual, and therapeutical data. The database was divided into two parts: a principal record, including information about the patient at the time of recruitment, and several follow-up records. Each patient received an identification number, and personal information was available only to principal investigators or co-investigators.

Periodic meetings were organized in order to make the recording process as homogeneous as possible for all centers. A manual procedure was developed, with detailed instructions and definitions needed for a correct compilation of the database. A copy of the structure of the database is available on request.

### Diagnostic criteria

A preliminary meeting of the principal investigators from each center was organized to select the clinical, biochemical, radiological, ophthalmological, and outcome parameters to be included in the database and to assess their definition. Tumor size was determined by CT scan or MRI of the sellar region. Tumors < 10 mm diameter were defined microadenomas and equal or greater than 10 mm macroadenomas. Depending on the information available in the principal record about neuroradiological characteristics of tumor (micro/macroadenoma, cavernous sinus invasion, sphenoid sinus invasion, optic chiasm compression, and stalk dislocation), adenomas were arbitrarily classified into grades I, II, III, and IV, indicating microadenoma, non-invasive macroadenoma, macroadenoma with invasion of one surrounding structure, and macroadenoma with invasion of two or more surrounding structures respectively. Central hypothyroidism was defined as low FT4 levels in the presence of inappropriate thyroid-stimulating hormone (TSH) levels. Central hypoadrenalism was defined as a lack of response to stimulation tests (peak cortisol levels lower than 500 nmol/l during 1  $\mu$ g adrenocorticotropic hormone (ACTH) test or insulin tolerance test). Central hypogonadism was diagnosed in the presence of low estradiol or testosterone levels and inappropriately normal or low gonadotropin levels. Growth hormone (GH) deficiency was diagnosed in the absence of adequate response to stimulation tests (peak GH levels lower than 3 or 9  $\mu$ g/l after insulin tolerance test or growth hormone-releasing hormone (GHRH) + arginine test respectively). Concomitant hyperprolactinemia was defined as prolactin (PRL) levels above the normal range and not consistent with the diagnosis of PRL-secreting adenoma. Hormonal values were interpreted according to the normal range of each laboratory.

Radiographic cure was defined as the absence of clear tumor remnants on the first post-operative (MRI) or (CT, if MRI scans were not available). Recurrence was defined as a detection of pituitary tumor in patients without evidence of residual tumor after surgical therapy, while regrowth was defined as an enlargement of tumor remnant at post-operative imaging.

**Statistical analysis**

All the quantitative variables are shown as mean  $\pm$  s.d. given the skewness of all variables time at the event, the comparison between different categories was made with Kruskal–Wallis test (16). The association between extension or grade of tumor and gender were studied using  $\chi^2$ - or the Fisher’s test for categorical variables (16). Analysis of cumulative incidence of recurrence or regrowth was made with Kaplan–Meier method, and differences among groups were tested with log-rank test. In all groups, the time from the surgery and the first recurrence or regrowth for elapsed patients and time from the surgery and the last follow-up for unelapsed patients were calculated. All the data analysis was made in STATA8 (StataCorp LP).

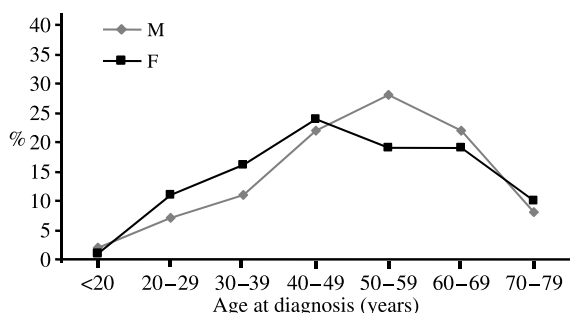
**Results**

**Patients population, symptoms, and hormonal alterations**

In the database, 295 patients (161 men/134 women) with a mean age of  $50.4 \pm 14.1$  years (range 14–78 years) and a mean time of follow-up of  $5.7 \pm 4.3$  years (range 2–28 years) were registered. No significant differences in the age at diagnosis ( $P=NS$ ), time of follow-up ( $P=NS$ ) and number of visits during the follow-up ( $P=NS$ ) between men and women were found. The diagnosis of NFPA was more frequently performed during the sixth decade of age for men and the fifth decade for women (Fig. 1).

Table 1 shows symptoms, hormonal alterations, neuroradiological, and visual findings at the time of diagnosis.

Most frequently, NFPA patients reported mass-related symptoms, such as visual deficit (67.8%) and headache (41.4%). Hypogonadal symptoms (i.e. loss of libido, impotence, oligo-amenorrhea) were observed in 42.5% of female and in 37.9% of male patients respectively (Table 1). At presentation, isolated or multiple pituitary deficits were diagnosed in 62% of patients. In particular, hypogonadism was the most frequent deficit reported (43.3%) and diabetes insipidus the rarest (1.9%) (Table 1). Concomitant



**Figure 1** Percentage distribution of age (decades) in non-functioning pituitary adenoma patients at the time of diagnosis ( $n=295$ ).

**Table 1** Symptoms, hormonal alterations, neuroradiological and visual findings in 295 patients with non-functioning pituitary adenomas at the time of diagnosis.

	% of patients
<b>Symptoms</b>	
Visual deficit	67.8
Headache	41.4
Asthenia	26.4
Loss of libido	28(M); 9.7(F)
Menstrual disorders	32.8
Galactorrhea	7.8
Impotence	9.9
<b>Hormonal alterations<sup>a</sup></b>	
Hypogonadism	43.3
GH deficiency	35.8
Hyperprolactinemia	27.6
Hypoadrenalism	26.2
Hypothyroidism	24.5
Diabetes insipidus	1.9
<b>Neuroradiological findings</b>	
Optic chiasm compression	45.4
Cavernous sinus invasion	33.2
Sphenoid sinus invasion	14.2
Stalk dislocation	12.2
<b>Grade<sup>b</sup></b>	
I	3.4
II	33.9
III	30.8
IV	31.9
<b>Visual findings</b>	
Campimetric alterations (right eye)	59.7
Campimetric alterations (left eye)	64.2
Loss of visual acuity (right eye)	24.8
Loss of visual acuity (left eye)	29.6

F, female; M, male.

<sup>a</sup>Percentages were relative to the patients for which these alterations were evaluated.

<sup>b</sup>I, II, III, IV, indicating microadenoma, non-invasive macroadenoma, macroadenoma with invasion of one surrounding structure, and macroadenoma with invasion of two or more surrounding structures respectively.

hyperprolactinemia was encountered in 27.6% of patients. No relationship between the presentation of the disease and the decade in which diagnosis occurred was observed (data not shown).

**Neuroradiological and visual findings**

Tumor extension was determined by CT scan or MRI. A macroadenoma was present in 96.5% of patients, causing optic chiasm compression and cavernous sinus invasion in a significant proportion of patients (45.4 and 33.2% respectively), without significant gender difference (Table 1). Tumors were equally distributed across grade II, III, and IV without significant sex-related differences ( $P=NS$ ). No relationship between the size and the invasiveness of the tumors and the decade in which diagnosis occurred was observed (data not shown).

Study of visual field was performed in 240/295 patients (81.4%). Visual field alterations were observed in the majority of patients and impairment of visual acuity in about one-third (Table 1).

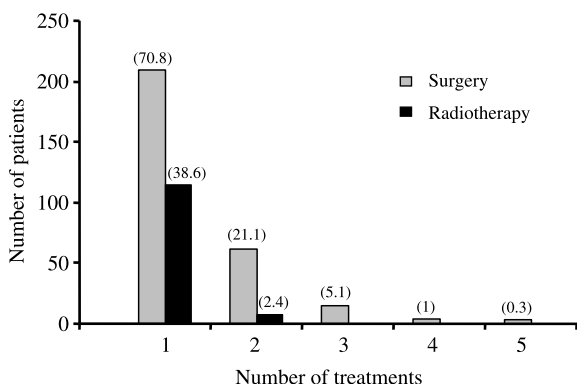
### Therapy and outcome

In all centers, the first choice treatment was neurosurgery performed in 268/295 patients (90.8%). The transsphenoidal route was performed in 89% of cases, while the remaining patients were treated by the transcranial approach. After a mean period of  $2.8 \pm 2.9$  years, 22 out of 27 patients, who initially received medical treatment with somatostatin analogs or had no treatment, were subsequently surgically treated. Therefore, 290/295 (98%) patients underwent surgery. On the basis of radiological findings, 105 surgically treated patients (35.5%) were considered cured (total tumor debulking). After a mean time of  $5.2 \pm 4.7$  years, 80 patients underwent one or more additional surgical treatments (Fig. 2).

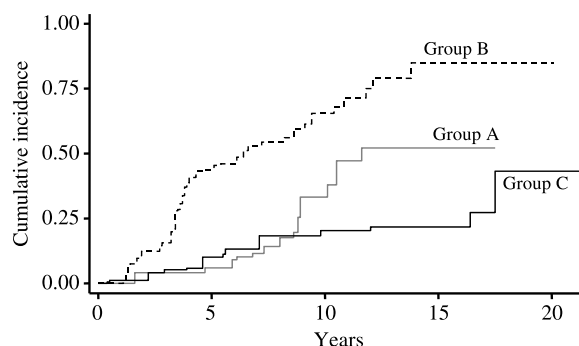
Radiotherapy was performed in 121 patients (41%). In all the cases, radiotherapy was used as adjuvant therapy after surgery. After a mean time of  $3.5 \pm 3.3$  years, 32 out of 121 patients were treated at entrance into our centers, while the remaining 89 were treated subsequently. The distribution of the total number of surgical and radiotherapeutic treatments in 295 NFPA patients is summarized in Fig. 2.

### Tumor recurrence or regrowth

Tumor recurrence or regrowth was investigated in 226 patients with a minimum follow-up of 5 years (mean follow-up  $9.3 \pm 4.3$  years, range 5.1–28 years). Seventy-three patients did not show neuroradiological evidence of residual tumor after surgical therapy (group A), 77 patients showed a post-operative tumor remnant, but did not undergo radiation therapy (group B) and 76 patients, with evidence of tumor remnant, were treated with radiotherapy after surgery (group C) (Fig. 3). Recurrence occurred in 14 out of 73 patients of group A (19.2%) after a mean period of

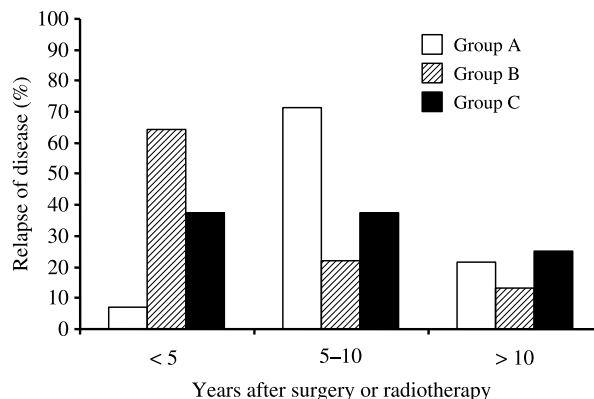


**Figure 2** Distribution of the total number of surgical or radiotherapeutic treatments in non-functioning pituitary adenoma patients ( $n=295$ ). The percentage of patients who underwent surgery or radiotherapy is indicated in parentheses.



**Figure 3** Cumulative incidence of recurrence or regrowth patients with non-functioning pituitary adenomas ( $n=226$ ). A indicates patients without postoperative tumor treatment, B, patients with tumor remnant who did not receive radiotherapy and C, patients with residual tumor treated with radiotherapy. The difference in the probability of recurrence or regrowth between the three groups was significantly different (Log-rank=119.83,  $df=2$ ,  $P>0.0001$ ), but with no difference between groups A and C (Log-rank=2.25,  $df=1$ ,  $P=NS$ ).

$7.5 \pm 2.6$  years (range 1.6–11.6 years), tumor regrowth in 45 out of 77 patients of group B (58.4%) after a mean period of  $5.3 \pm 4.0$  years (range 1.1–20.3 years), and in 14 out of 76 (18.4%) patients of group C after a mean period of  $8.1 \pm 7.3$  years (range 0.4–25.5 years). Analysis of cumulative incidence showed a significant difference in the probability of recurrence or regrowth among three groups (log-rank=119.83,  $df=2$ ,  $P<0.0001$ ), with no difference between group A and C (log-rank=2.25,  $df=1$ ,  $P=NS$ ; Fig. 3). Collectively, tumor regrowth of group B patients peaked after a time interval of <5 years, recurrence of group A patients after a 5–10 years interval, while tumor enlargement after radiotherapy in group C occurred equally across the follow-up period (Fig. 4).



**Figure 4** Time distribution of percentage of tumor recurrence or regrowth in patients with non-functioning pituitary adenoma ( $n=226$ ). A indicates patients without postoperative tumor treatment, B, patients with tumor remnant who did not receive radiotherapy and C, patients with residual tumor treated with radiotherapy.

## Discussion

This is the first reported database that collected clinical, biochemical, radiological, ophthalmological, and outcome data specifically focused on NFPAs in Europe. The aim of this database was to provide retrospective information on demographic, clinical and biochemical presentation, therapeutic approaches, and long-term outcomes in patients with NPPA. The ultimate goal is to improve the management of these tumors. Admittedly, since most the centers participating in this project were centers of major teaching and general hospitals and most patients were referrals from other specialists, it is conceivable that the registered data might be pertinent to patients with more complex diseases and not to the overall population of NFPAs. Analysis of the registered data (i.e. the tumor size, the symptoms due to the mass effect and the similar presentation of the disease over time) indicated a dramatic delay in the diagnosis of NPPA, despite the improvement of the currently available biochemical and neuroradiological techniques. In fact, almost all the patients of our series harbored macroadenomas that were mainly diagnosed between the fifth and the seventh decade. Moreover, invasion of the surrounding structures was present at diagnosis in two-third of patients. These data are consistent with many reports (1, 3–5, 17), but partially in contrast to the information collected in the only other available pituitary tumor registry in US, reporting that age at diagnosis of NFPAs peaked across the fourth and the fifth decade and showing a higher prevalence of microadenomas (32%) in women (18). NFPAs presented in about half of the patients with mass-related symptoms, as visual defects, headache, and hypogonadism symptoms. Unfortunately, these signs are still underestimated or not correctly diagnosed, especially considering the mean age of patients at diagnosis. Therefore, the reduction of the delay between symptom onset and diagnosis still represents a challenge for endocrinologists, gynecologists, andrologists, ophthalmologists and, particularly, general practitioners.

One-fourth of patients had mild hyperprolactinemia, typically related to stalk deafferentation, while single or multiple pituitary deficits were diagnosed in 62% of patients before surgery, in agreement with previous reports (5, 18, 19). Admittedly, the percentage of patients with pituitary deficit was probably underestimated because some functions, in particular GH secretion, were not routinely evaluated in the past.

As expected, surgery represented the first therapeutic approach. Radiological cure, defined as the absence of tumor remnants on neuroradiological imaging, was achieved in 35.5% of patients. This result, that is in agreement with previous studies (4, 5, 18), was related to the large size of almost all NFPAs at diagnosis. Moreover, it is worth noting that about one-third of not cured patients in our database underwent one or more additional surgical treatments. Failure of

surgical treatment caused a frequent indication for conventional or stereotactic radiotherapy that was performed in about 40% of patients. However, the role of conventional radiotherapy in pituitary tumor management remains controversial. Although its efficacy in reducing recurrence or regrowth of tumor remnants, in particular if administered during post-operative period, has been demonstrated (1, 3, 6), this therapy may cause several side effects, as hypopituitarism, increased risk of second brain tumor, neurocognitive, or neuropsychological impairments (20–23). New radiation techniques, such as Gamma Knife radiosurgery, have shown in the short-term to have a good efficacy in controlling tumor growth and a more favorable profile of side effects than conventional fractionated radiotherapy (24, 25).

As far as the long-term outcomes of patients registered in our database were concerned, patients without post-operative residual tumor and patients who underwent adjuvant radiotherapy showed a similar risk of tumor recurrence or regrowth (reported in 19.2 and 18.4% respectively), while tumor remnant regrew in 58.4% of patients who did not receive radiotherapy. These data are in agreement with previous reports (1, 2, 5, 26, 27). Some interesting information arises from the different time of occurrence of regrowth or recurrence. In particular, tumor enlargement after radiotherapy occurred all along across the follow-up periods, while recurrence in cured patients peaked after 5–10 years from surgery. These data suggest that a close follow-up, with serial MRI every 12–18 months, is necessary for at least 10 years in all patients, followed by a follow-up based on clinical indications. In this respect, administration of dopamine agonists associated or not with octreotide analogs has been proposed as adjuvant treatment for patients with NFPAs unsuccessfully treated by surgery (28–30).

Patients with NFPAs have an increased mortality, mainly due to respiratory, cardiovascular, and cerebrovascular diseases, that seems to be related to several factors, including surgery, untreated hypopituitarism, and radiotherapy (31–38). Our database clearly indicates that the goal of a definitive surgical cure, without subsequent radiotherapy and with preservation of normal residual pituitary functions, has been achieved during the last decade in a low percentage of patients, even when followed in highly qualified endocrine centers.

In conclusion, data collected in our database give a complete overview of patients with NPPA in term of clinical debut, therapeutic approaches, and long-term outcomes. This tumor database may help to reduce the delay between symptom onset and diagnosis, to assess prognostic parameters for the follow-up of patients with different risk of recurrence and to define the efficacy and safety of different treatments and their association with mortality/morbidity. Moreover, the relatively large number of cases recorded in our database may be used prospectively to evaluate clinical and diagnostic

progresses and to improve therapeutic guidelines and overall cost-effectiveness in the long-term management of NFPAs.

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