RESEARCH

Natural history and surgical outcome of incidentally discovered clinically nonfunctioning pituitary macroadenomas

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Abstract

Objectives: The incidental diagnosis of nonfunctioning pituitary macroadenomas (NFPMAs) is becoming more prevalent with the spread of modern brain imaging techniques. We sought to uncover new data about their natural history and surgical outcome.
Design: This is a retrospective single-center observational study.
Methods: Among 210 patients seen for a NFPMA between 2010 and 2019, 70 (33%) were discovered incidentally (i-NFPMA). We analyzed outcomes in a total of 65 patients with available follow-up data.
Results: Mean age at diagnosis (± s.d.) was 60 ± 14 years and mean maximal diameter was 20.0 ± 7.3 mm. At diagnosis, 29 patients (45%) had pituitary hormone deficits (LH/FSH 41%, TSH 29%, ACTH 15%) and 12% had visual field deficits. 26 patients underwent initial surgery, while 12 had delayed surgery after initial surveillance. In the surveillance group, the risk of tumor growth was estimated at 10%/year. Patients with hormonal deficits at diagnosis experienced earlier growth at 24 months ($P < 0.02$). Overall, surgical resection of the i-NFPMA led to stable or improved endocrine function in 91% of patients, with only 6% postoperative permanent diabetes insipidus. Moreover, surgery was more effective in preserving intact endocrine function (10/12) than restoring altered endocrine function to normal (6/22, $P = 0.03$).
Conclusion: About one-third of NFPMAs are now discovered incidentally and a significant subset may be responsible for unrecognized endocrine and visual deficits. Under surveillance the risk of further tumor growth is significant (10%/year) and seems to occur faster in patients already harboring an endocrine deficit. Early surgical removal before onset of endocrine deficits appears to lead to better endocrine outcome.

Keywords

- pituitary neuroendocrine tumor
- pituitary incidentaloma
- nonfunctioning pituitary adenoma
- pituitary deficits
- neurosurgery

Endocrine Connections (2023) **12**, **e230224**

Introduction

Pituitary incidentalomas (PIs) are lesions of the pituitary gland discovered during an imaging procedure performed for reasons unrelated to the lesion itself. Most frequently, these are clinically nonfunctioning pituitary adenomas (1) (NFPAs). Even though radiological and autopsy studies find mostly small pituitary microadenomas (2, 3, 4) (<1 cm), recent case series revealed that more than half of PIs coming to medical attention are macroadenomas (5, 6, 7, 8, 9, 10, 11). Moreover, a significant subset of these patients with incidentally discovered nonfunctioning pituitary macroadenomas (i-NFPMA) harbor unrecognized

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pituitary hormone deficits (24–36%) and visual deficits (9–36%) (5, 6, 7, 8, 9, 10, 11).

The guidelines on the management of PIs by the Endocrine Society date back to 2011 (6). They recommended complete clinical and biological evaluation of all patients with incidental macroadenomas, and visual evaluation for those whose tumor is abutting or compressing the optic chiasma. Surgery is clearly necessary for GH and ACTH secreting tumors, for lesions leading to visual deficits related to chiasma compression or neurological compromise and medical treatment with dopamine agonists is advised in incidental PRL-secreting macroadenomas. In all other cases, surveillance is a viable option, with initial clinical, biological, and radiological follow-up intervals of 6 months to one year that may become longer with time. Time-related tumor growth, younger age, hormone or visual deficits, as well as unremitting headache are recognized indications for surgery, although they need to be discussed on a case by case basis by a specialized multidisciplinary pituitary team (6).

When facing a PI that does not meet clear-cut criteria for surgery, clinicians encounter one unresolved question: is it best to simply wait and see if the tumor will grow, thus avoiding any complication of surgery, or is it best to remove it as soon as possible, to avoid any future pituitary or visual deficit related to tumor growth and potentially riskier surgery? Recent studies showed that 23–27% of macroincidentalomas will grow over a period of 2–5 years (5, 7, 8). However, the risk of growth rises with time and a recent meta-analysis reported a 12.5% yearly risk of long term growth for incidental macroadenomas (9). Factors that could predict future growth or visual and/or hormonal compromise are not well known, and studies comparing surveillance versus early surgery are scarce.

We analyzed our own cohort of i-NFPMA, in order to obtain more epidemiological data about their presentation, natural history and surgical outcome. Furthermore, we also sought to identify factors that can predict tumor growth in patients that did not undergo initial surgery and to study the influence of preexisting endocrine deficits on surgical results.

Methods

Population

We retrospectively analyzed medical files of all patients referred to our endocrine clinic for a pituitary nonfunctioning macroadenoma (NFPMA) between 2010 and 2019. In agreement with the guidelines of the Endocrine Society, they were considered incidental (i-NFPMA) if initial imaging had not been performed for reasons attributable to the lesion itself, such as visual field deficit, oculomotor nerve palsy, acute and intense headache in case of apoplexy, or hormonal anomalies compatible with pituitary insufficiency (6).

Clinical evaluation

We carefully reviewed the initial presentation to determine if patients were symptomatic at diagnosis, even if those symptoms had not been previously attributed to the pituitary adenoma. We also analyzed if patients suffered from pituitary hormone or visual field deficits, even though they did not complain about any symptoms. Weight gain was considered related to NFPMA if central hypogonadism or central hypothyroidism was present. Menstrual disorders and sexual dysfunction were attributed to NFPMA only if central hypogonadism was present. Weakness was considered as potentially due to NFPMA in case of any pituitary hormone deficiency.

Endocrinological and ophthalmological evaluation

We evaluated endocrine status by serum levels of pituitary hormones with no systematic dynamic testing. We did not evaluate adult GH deficiency in the absence of another pituitary deficit (as acquired isolated adult GH deficiency is not reimbursed in Belgium) and therefore did not include adult GH deficiency in our analysis. Gonadotropin insufficiency was defined, in men, by a low morning testosterone level on two separate occasions along with low or low normal LH and FSH; in premenopausal women, by oligomenorrhea or amenorrhea and low estrogen levels along with low or low normal LH and FSH; and in menopausal women, by the absence of elevation of LH and FSH. Thyrotropin deficiency was defined by a low free T4 concentration combined with nonelevated TSH levels. Corticotropic deficiency was defined by a low morning cortisol below 138 nmol/L which has been described as a good cutoff for ACTH deficiency (10). Visual field deficits secondary to compression by the NFPMA were determined on a complete evaluation by a specialized neuro-ophthalmologist.

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Patient were deemed deficient if they suffered from an objective hormonal or visual deficit, whether symptomatic or not. As such, some patients were asymptomatic (they had no subjective complaints) but were found to have objective deficits.

Radiological evaluation

All patients underwent a dedicated 1.5 or 3.0 Tesla pituitary magnetic resonance imaging (MRI), with acquisition of coronal and sagittal sections of T2-weighted images and T1-weighted images before and after gadolinium injection. Growth was defined as an increase of at least 2mm in any dimension.

One single reader (TD) compared the different MRIs, not only with the previous one but also with the baseline diagnostic examination. After diagnosis, the first MRI was performed at 6 months in case of chiasmal contact/proximity or after one year if there was no suprasellar extension. After the initial follow-up, if the tumor was stable, follow-up intervals were extended progressively to 1, 2, and then 3 years. After surgery, the first MRI was performed after 3–6 months, and subsequent controls were more frequent if a residue was present and the tumor was proliferative at immunohistochemistry.

Subgroup analysis

Initial surgery was defined as the decision of the Pituitary team to perform surgery immediately after the initial evaluation of the NFPMA. In these cases, surgery was usually performed within the first 6 months after diagnosis. We analyzed the characteristics of the entire cohort, and then compared patients according to several criteria: patients who suffered from tumor growth during follow-up versus those who did not, and surgical results in deficient versus nondeficient patients (objective endocrine or visual impairment).

Statistical analysis

Statistical analyses were performed using SPSS® (IBM®) version 27.0. Results are shown either as mean ± standard deviation or median and percentiles 5–95. Comparisons of categorical unpaired variables between subgroups were performed using Pearson's χ^2 tests or Fisher's exact tests. Student's *t*-test was used for comparing means of continuous unpaired variables. Tumor growth-free evolution was analyzed by the Kaplan–Meier survival method, and the log-rank test was used to compare evolution between subgroups of patients. Statistical significance was set as a $P < 0.05$ (bilateral).

Ethics

The study was approved by the Ethics Committee of Saint Luc University Hospital and patient's informed consent was waived due to the retrospective design of the study. All data were handled according to national laws and European general data protection regulation.

Results

Population characteristics

Among 210 patients with a NFPMA seen at our clinic between 2010 and 2019, 70 (33%) were discovered incidentally. Among them, five patients were excluded because of incomplete medical files and follow-up. Thus, 65 patients (28 women and 37 men) were included in the study.

The mean age at diagnosis was 60.0 ± 14.3 years. Computerized visual field evaluation demonstrated visual field defects in eight out of the 36 patients with chiasmal contact of the tumor. Of note, only one of the eight patients had subjective perception of the defect.

Twenty-four (37%) patients complained of headache. The mean maximal tumor diameter was 20.0 ± 7.3 mm and was not significantly different ($P = 0.80$) among those who did not report headache as a symptom (20.2 ± 7.0 mm) and those who did (19.7 ± 7.5 mm). There was also no statistically significant difference between those who had headache or not in terms of mean tumor height, width, length or coronal surface, or cavernous sinus invasion (data not shown).

As regards endocrine self-reported symptoms, 13 out of the 65 patients had at least one subjective complaint. After objective endocrinological evaluation, only eight out of 13 had pituitary hormone deficiency that could explain their complaints (weakness and weight gain in four patients, sexual dysfunction in three patients, and menstrual disorders in one patient).

Neurologists (18%), family doctors (17%), ENT specialists (15%), and internal medicine specialists (12%) were the most common prescribers of imaging leading to incidental diagnosis of the NFPMA.

Radiological, endocrinological, and ophthalmological evaluation at diagnosis

The results of MRI, visual field testing and pituitary hormone measurements are summarized in Table 1. On pituitary MRI, 22 patients (34%) suffered from cavernous sinus invasion. 36 (55%) exhibited contact with the optic chiasma and in 20 (31%) the tumor led to chiasmal displacement. In the latter group, 8 patients had visual field defects, and 13 patients underwent surgery.

Based on the hormonal workup, 29 patients (44%) suffered from at least one pituitary hormone deficiency. As expected, the most common deficit was LH/FSH deficit (41%) followed by TSH deficit (29%). An increase in PRL concentrations was observed in 26 patients (40%), but was usually of modest amplitude (median of 1.53 × the upper limit of normal (ULN); maximal value of 9.73 × ULN).

Overall, 34 patients had intact visual fields and pituitary functions, 25 had either visual or hormonal deficits, and 6 had both visual and hormone deficits.

Management

After the initial evaluation, 26 patients were referred for surgical removal of the NFPMA, generally within 6 months, mostly for chiasmal contact/compression (13/26).

The 39 other patients were simply followed by regular MRI and biological workups. Among those 39, after excluding 4 patients lost to follow-up, 19 out of 35 patients experienced tumor growth, and of these, 12 required surgery and 1 was treated with conventional fractionated radiotherapy because of contraindications to surgery. The six other patients elected to remain under surveillance because the growth was moderate (mean of 4 mm during the follow-up period) and did not provoke any new visual deficit (Fig. 1).

The only patient with visual deficit at diagnosis that did not undergo surgery was 89 years old with a 20 mm tumor discovered incidentally after a fall. Given the patient's age and the asymptomatic nature of the visual field deficit, simple surveillance was conducted.

Table 1 Radiological, endocrinological, and ophthalmological evaluation in the total cohort of patients with an incidentally found NFPMA (for whom data were available at diagnosis; $n = 65$).

	Total cohort ($n = 65$)
Radiological and visual evaluation	
Mean maximal diameter (mm)	20.0 ± 7.3
Cavernous sinus invasion	22/65 (31%)
Chiasmal contact	36/65 (55%)
Visual deficits	8/65 (12%)
Endocrine evaluation	
Any pituitary deficit	29/65 (44%)
LH/FSH deficit	27/65 (41%)
TSH deficit	19/65 (29%)
ACTH deficit	10/65 (15%)
PRL elevation	26/65 (40%)
PRL (×ULN) if PRL elevation present	1.53 (1.1–3.1)
Diabetes insipidus	0/65 (0%)

ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PRL, prolactin; TSH, thyroid-stimulating hormone; ULN, upper limit of normal.

Follow-up

Tumor growth

As mentioned, 19 out of 35 patients had tumor growth during a median radiological follow-up of 50 (6–122) months. The median size increase during follow-up was 5 (2–10) mm, and growth occurred after a median of 49.7 (13.7–98.7) months. The percentage of patients experiencing growth was 14% after 2 years, 29% after 4 years, and 51% after 5 years. The median duration to reach 50% of patients with tumor growth was 57 months (43–71). During follow-up, the median tumor size increase was 0.9 mm/year (0.3–3.9 mm/year), with a wide range of progression as shown in Fig. 2.

We compared the cumulative incidence of growth between pituitary hormone deficient and nondeficient patients. There was no significant difference in the overall probability of tumor growth over the follow-up period (Fig. 3; log-rank $P = 0.082$). We did, however, observed a significant difference in the delay to growth occurrence: deficient patients experienced growth earlier than nondeficient patients. After 2 years, 4 out of 10 patients who initially had endocrine deficits experienced growth compared to only 1 out of 25 of nondeficient patients ($P < 0.02$). After 5 years, all patients who initially had hormonal deficits had experienced tumor growth, compared to only 60% of the nondeficient subjects (NS). There was no significant difference in growth rate between patients with cavernous sinus invasion at diagnosis and those without ($P = 0.11$).

We also compared patients who experienced growth during follow-up with patients who did not, in order to find clinical, radiological, or biological characteristics that could predict future growth (Supplementary Table 1, see section on supplementary materials given at the end of this article). We did not find, however,

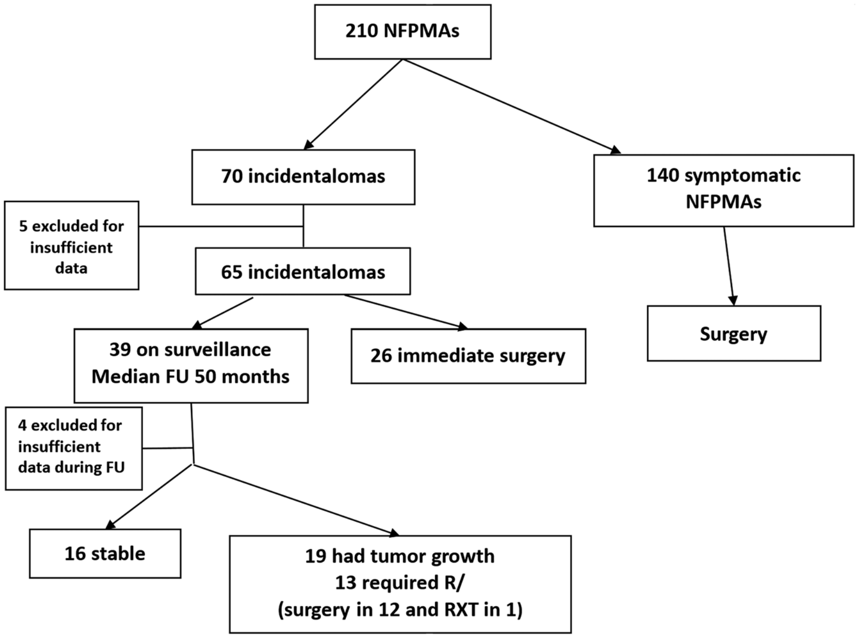

Figure 1
Study flowchart: details of patient inclusion and patients analyzed for subsequent management. FU, follow-up; RXT, radiotherapy.

any statistically significant difference between the clinical, radiological, or biological characteristics of these two subgroups. Younger age (P=0.16) showed a nonsignificant tendency toward more frequent tumor growth, while initial tumor size was similar.

Endocrine and visual function

Among the 35 patients initially managed conservatively, 12 required surgery and one radiotherapy. Up until last follow-up or until surgery and radiotherapy, only four patients developed a new hormonal deficiency (two gonadotropin deficits, two thyrotropin deficits) and all belonged to the nonsurgical group. Only one patient developed a new visual deficit that was reversed after surgery.

Surgery

Overall, 38 patients underwent surgical resection (early surgery in 26 and delayed surgery in 12, Fig. 1). The mean maximal tumor diameter at surgery was 23.4 ± 6.6 mm. The indications for surgery were most commonly visual compression (42%), large adenoma size and young age (22%), threatening chiasmal contact (14%), and tumor growth (11%).

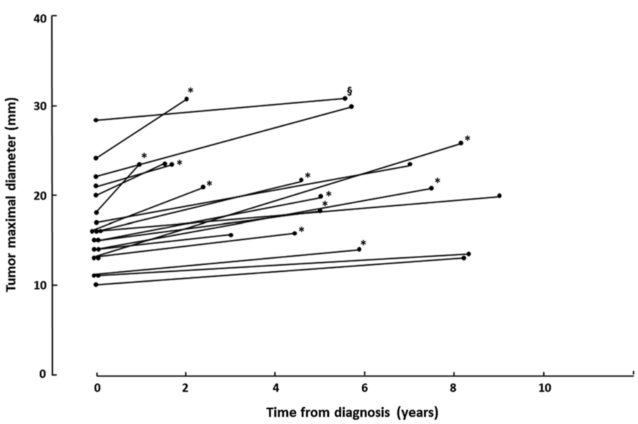

Figure 2
Evolution over time of tumor maximal diameter (mm) in patients with a nonfunctioning pituitary macroincidentaloma undergoing first surveillance after diagnosis at time 0 and until surgery (*), radiotherapy (§) or last follow-up pituitary imaging. Tumor growth rate was assumed to be a constant over time for clarity.

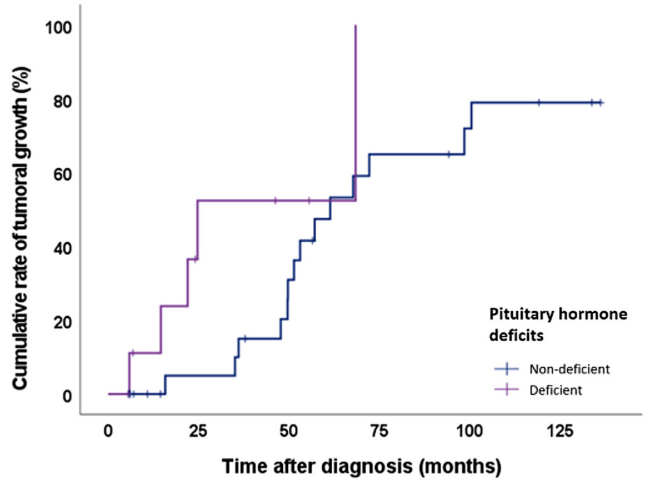

Figure 3
Cumulative incidence of tumor growth during follow-up according to the presence of endocrine deficits at diagnosis.

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Table 2 Endocrine function following surgery.

	At surgery (*n* = 34)	After surgery[a] (*n* = 34)	New postoperative deficit (*n* = 34)
LH/FSH deficit	20/34	12/34	0/34
TSH deficit	14/34	14/34	2/34
ACTH deficit	7/34	4/34	0/34
Diabetes insipidus	0/34	2/34	2/34
PRL elevation	14/34	2/28[b]	–

[a]Median of 8 months (range 1–16) after surgery; [b]*n* = 30 with available PRL level at follow-up.
ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PRL, prolactin; TSH, thyroid-stimulating hormone; ULN, upper limit of normal.

Follow-up endocrine data were available for 34 patients after surgery (Table 2). After a median of 8 months after surgery (range: 1–16 months), 8/34 had improved gonadotrope function, 2 out of 34 patients had improved thyrotrope function, and 3 out of 34 patients had improved corticotrope function. The number of hyperprolactinemic patients decreased from 40% to 7% after surgery. After surgery, three patients developed new deficits: diabetes insipidus alone in one patient, diabetes insipidus and TSH deficit in one patient, and TSH deficit alone in another patient.

The histoimmunological nature of operated i-NFPMA revealed mostly gonadotroph (17/34, 50%) and immunonegative adenomas (11/34, 32%), but it must be emphasized that no immunohistochemistry was performed for transcription factors such as SF-1 that would likely have reclassified a majority of these in gonadotroph cell-lineage adenomas. We also identified three silent ACTH adenomas and one silent PRL adenoma. When available, histological markers were as follows: positive P53 expression in 13/28, mitosis in 0/14, Ki67 > 3% in 12/31.

Complications of surgery were fairly common but reversible: transient diabetes insipidus in 15%, preoperative repaired CSF leak in 15%, postoperative hyponatremia and epistaxis in 3% each. Only 2 out of 34 patients (6%) developed permanent diabetes insipidus. After a median postsurgical radiological follow-up of 9 (3–17) months, 17/34 patients had a residual tumor on MRI (50%). Twenty patients had postoperative visual assessment: Four (20%) had visual improvement and the other patients had stable visual function.

Finally, we sought to compare surgical results in patients with visual or hormonal deficits at the time of surgery and those without (Table 3). Deficient patients at surgery had larger tumors (maximal diameter 25.0 ± 6.3 mm versus 20.7 ± 6.4 mm, $P = 0.058$). There was no significant difference between these groups in residual tumor prevalence at 1 year (12/22 vs 5/12). One year after surgery, significantly more patients without deficit at surgery had normal endocrine function (10/12 versus 6/22 of patients with any deficit at surgery, $P = 0.03$).

Discussion

We describe here a large cohort of 65 patients with an incidentally discovered clinically nonfunctioning

Table 3 Comparison between the group of patients without any deficit at surgery and the group of patients with a visual and/or hormonal deficit at surgery.

	No deficit at surgery (*n* = 12)	Visual or hormonal deficit at surgery (*n* = 22)	*P*
Age	55.0 ± 7.6	61.0 ± 13.3	NS
Delay from diagnosis to surgery (months)	21 (4–83)	4 (1–84)	0.016
Maximal diameter at surgery (mm)	20.7 ± 6.4	25.0 ± 6.3	0.058
Height at surgery (mm)	16.0 ± 4.1	24.2 ± 6.3	0.0001
Width at surgery (mm)	19.5 ± 7.4	21.3 ± 5.9	NS
Length at surgery (mm)	14.6 ± 2.7	20.0 ± 4.1	0.001
PRL/ULN at surgery	0.8 (0.4-1.4)	1.0 (0.4-3.0)	0.035
Ki-67 (% of cells)	2.4 ± 0.9	2.4 ± 1.3	NS
Complications of surgery	7/12	7/22	NS
Residual tumor at 1 year after surgery	5/12	12/22	NS
PHD at 1 year after surgery (New/stable/resolved)	2/10/0	1/13/8	0.04
Diabetes insipidus at 1 year after surgery	1/12	1/22	NS
Absence of PHD 1 year after surgery	10/12 (83%)	6/22 (27%)	0.03
Visual field improvement 1 year after surgery	NA	4/13	NA

Data are shown either as mean ± s.d. or median (percentile 5–95).
ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PHD, pituitary hormone deficit; PRL, prolactin; TSH, thyroid-stimulating hormone; ULN, upper limit of normal.

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pituitary macroadenoma, showing that they represent about one-third of all NFPMA referred to our tertiary endocrine center during a 10-year period, and that they may cause asymptomatic or pauci-symptomatic endocrine and visual field deficits in a significant proportion of cases (45% and 12%, respectively). The mean age at discovery was 60 years with the most frequent endocrine deficits being LH/FSH (41%) and TSH (29%) insufficiency, keeping in mind that GH deficiency was not routinely assessed. A majority of these i-NFPMA (55%) made contact with the optic chiasma and 40% underwent surgical removal after the initial workup.

These results are similar to those of recent incidentaloma series reported in the literature, with a mean age of discovery of 52–61 years, and a prevalence of pituitary hormone deficits of 24–36% and of visual deficits of 9–36% of patients (5, 7, 11, 12, 13, 14, 15). These numbers underscore the importance of raising awareness among all medical practitioners that such lesions, although discovered incidentally, must be referred for further evaluation. Surgical removal rates in recent published series of PI as a whole (not limited to NFPMA) ranged between 29 and 32% (5, 11, 16).

The diagnosis of NFPMA may be unrecognized for a long period of time, as most are asymptomatic or have symptoms that are either not related to the tumor itself or nonspecific. Strikingly, even though eight patients had visual field deficits in our series, only one had subjective complaints clearly related to chiasmal compression, underscoring the silent nature of these tumors and the risk of unnoticed tumor expansion. Careful endocrinological evaluation of these patients is also paramount, as we found that 29 out of 65 patients had silent TSH and/or ACTH insufficiency, the latter being able to severely impact health outcomes if ignored and left untreated.

Regarding management, not all patients who underwent surgery initially had visual deficits, and young age was an important factor in the initial management decision. Indeed, the presence of a large macroadenoma in an otherwise healthy 40- to 60-year-old patient often constitutes a reasonable indication for surgery. The cumulative risk of growth and visual and endocrine deterioration is often considered as a reason to operate. To illustrate this point, in our cohort of patients who underwent surgery without any visual or endocrine deficit, the mean age was 55 and the mean tumor diameter was 20 mm. Currently there are no recognized age or size cutoffs to guide clinicians. Radiological and endocrinological follow-up is essential if surveillance is chosen, but the same is true after surgery. Surveillance after surgery should, however, be tailored according to the presence of a residue and proliferative characteristics of the tumor (Ki67 >3%, mitosis >10/field, high p53 expression) (17). The availability of an experienced pituitary surgeon is also crucial, as recent studies have shown a clear improvement in remission rates and complications for centers with >25 surgeries per year (18).

In the subgroup of patients left on surveillance, we showed an overall annual growth rate of about 10% (50% at 5 years), which is in line with growth rates reported in the general NFPMA literature (whether asymptomatic or not). We observed higher growth rates as the follow-up gets longer (17% for follow-up <4 years and 34% for follow-up 5–8 years in the review by Huang and Molitch (8) and 12.5% per year in the meta-analysis by Fernández-Balsells *et al.* (9)). It is, however, slightly higher than those reported in other incidentaloma cohorts (23–33% (5, 7, 19)). Selection bias might explain this difference: other studies sometimes looked at all types of pituitary incidentalomas (including Rathke's cleft cysts or meningiomas) that might grow less. In addition, the initial tumor size differs between studies and smaller NFPMA (10–15 mm) might not have been referred to our center. Another common bias in all these studies is the likelihood of follow-up loss in patients with a nonsymptomatic and quiescent pituitary incidentaloma. However, this loss of follow-up rate was low in our study. Of note, we did not find any clinical, biological, or radiological predictive factor clearly associated with the risk of tumor growth in these patients (although younger age showed a tendency to be associated with tumor growth). This is in keeping with the current literature, where no known predictor of growth exists a part from the size of the adenoma itself (19, 20, 21).

To the best of our knowledge, we analyzed for the first time the presence of endocrine deficits at diagnosis as a risk factor of growth in patients with incidental NFPMA. Although the presence of deficits did not influence the overall risk of tumor growth during the follow-up period, it was associated with a more rapid growth if progression was present. This result should prompt clinicians to follow such patients more regularly, at least during the two first years of follow-up.

Surgical results in our series are in keeping with the current literature, with an overall rate of tumor residue

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of about 50% (22) and low rates of severe permanent complication (no death; 6% diabetes insipidus) (23, 24). In contrast with previous studies (25, 26), we did not find significantly less postoperative residue in patients who had surgery with no deficits. These conflicting results might be related to the small size of our surgical cohort and to the high prevalence of cavernous sinus invasion, which was expectedly associated with the presence of postoperative residue.

However, we confirm a significant advantage of early surgery in sparing pituitary hormonal axes, as described by other studies (25, 26). More than 80% of patients with normal preoperative endocrine function can hope to retain normal endocrine function after surgery, compared to only a quarter of patients recovering normal function if they a had a preexisting endocrine deficit before surgery. Furthermore, conservative management was associated with a need for later surgery in 30% of patients, with 14% of patients suffering from new endocrine deficits and 5% from new visual deficits. However, these incidences are for our cohort as a whole, and not specifically for those with no initial endocrine deficit. We did not design our study to compare outcomes between early surgery and conservative management for nondeficient patients, which would have necessitated a prospective comparative design.

Limitations of our study include the small number of patients, which lowers the power of our statistical analysis, as well as its retrospective nature, which restricts the depth and precision of data collection. As we did not look for GH deficiency, the incidence of NFPMA related weakness in our cohort might also be underestimated. Other limitations include the lack of data collection on tumor recurrence after surgery, substitutive hormonal treatment, and the relatively short duration of follow-up. In contrast, strengths of our study include a relatively large number of patients included in the whole cohort, the careful and complete radiological, endocrinological, and ophthalmological evaluation, and the evaluation of the impact of deficits on growth speed in conservatively managed patients.

In conclusion, in a cohort of 65 patients with an incidentally diagnosed pituitary clinically nonfunctioning macroadenoma, we show a significant prevalence of unrecognized endocrine and visual deficits, leading to initial surgery in 40% of patients, thus confirming the need for a careful evaluation of such patients. In conservatively managed patients, we observed an annual growth rate of 10%, and the initial presence of an endocrine deficit was associated with a shorter time to progression. Our data also suggest that patients who undergo surgery with a normal endocrine function benefit from a better endocrine outcome compared to those who already had a preexisting endocrine deficit.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EC-23-0224.

Declaration of interest

We have no conflict of interest to declare.

Funding

No funding to declare.

Author contribution statement

S.M.C., O.A., and D.M. followed patients in the endocrine clinic and collected the data. S.M.C performed statistical analyses and wrote the first draft. E.F. and C.R. performed all surgeries. T.D. was responsible for analyzing MR imaging. All authors revised the final manuscript.

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Received 6 June 2023
Accepted 2 October 2023
Available online 6 October 2023
Version of Record published 27 October 2023