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Original Research

Natural history of non-functioning pituitary microadenomas: results from the UK non-functioning pituitary adenoma consortium

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Abstract

Objective: The optimal approach to the surveillance of non-functioning pituitary microadenomas (micro-NFPAs) is not clearly established. Our aim was to generate evidence on the natural history of micro-NFPAs to support patient care.

Design: Multi-centre, retrospective, cohort study involving 23 endocrine departments (UK NFPA consortium).

Methods: Clinical, imaging, and hormonal data of micro-NFPA cases between January, 1, 2008 and December, 21, 2021 were analysed.

Results: Data for 459 patients were retrieved [median age at detection 44 years (IQR 31-57)—152 males/307 females]. Four hundred and nineteen patients had more than two magnetic resonance imagings (MRIs) [median imaging monitoring 3.5 years (IQR 1.71-6.1)]. One case developed apoplexy. Cumulative probability of micro-NFPA growth was 7.8% (95% CI, 4.9%-8.1%) and 14.5% (95% CI, 10.2%-18.8%) at 3 and 5 years, respectively, and of reduction 14.1% (95% CI, 10.4%-17.8%) and 21.3% (95% CI, 16.4%-26.2%) at 3 and 5 years, respectively. Median tumour enlargement was 2 mm (IQR 1-3) and 49% of micro-NFPAs that grew became macroadenomas (nearly all >5 mm at detection). Eight (1.9%) patients received surgery (only one had visual compromise with surgery required >3 years after micro-NFPA detection). Sex, age, and size at baseline were not predictors of enlargement/reduction. At the time of detection, 7.2%, 1.7%, and 1.5% patients had secondary hypogonadism, hypothyroidism, and hypoadrenalism, respectively. Two (0.6%) developed hypopituitarism during follow-up (after progression to macroadenoma).

Conclusions: Probability of micro-NFPA growth is low, and the development of new hypopituitarism is rare. Delaying the first follow-up MRI to 3 years and avoiding hormonal re-evaluation in the absence of tumour growth or clinical manifestations is a safe approach for micro-NFPA surveillance.

Keywords: non-functioning, pituitary, adenoma, natural history, incidentaloma

Significance

In the largest study to date involving 23 endocrine departments, we have elucidated the natural history of non-functioning pituitary microadenomas providing data to inform surveillance protocols. The probability of tumour growth was 7.8% and 14.5% at 3 and 5 years, respectively. Overall, 0.2% of the total group developed visual compromise due to tumour growth, and 1.9% received pituitary surgery following tumour enlargement. Our data challenge existing guidelines and provide evidence to promote the extension of initial imaging surveillance to 3 years after non-functioning pituitary microadenoma detection. New hypopituitarism occurred in only 0.6% of patients; therefore, repeat hormonal evaluation in the absence of tumour growth or relevant clinical manifestations is not routinely required. These data are reassuring for patients and clinicians alike.

Introduction

Non-functioning pituitary adenomas (NFPAs) are benign pituitary tumours not associated with clinical manifestations secondary to hormonal hypersecretion.[1] Their prevalence is reported between 7 and 41.3 per 100 000 population.[2,3] Presentation arises once the NFPA has grown large enough to cause compression of nearby structures, or, as increasingly observed, when incidentally detected by cranial imaging performed for unrelated reasons.[4] Non-functioning pituitary microadenomas (micro-NFPAs) have a maximum diameter of <1 cm and, given their small size, tend to be incidental findings. In radiological series, 10%-38% of healthy people with no previous known history of pituitary disease have pituitary abnormalities on magnetic resonance imaging (MRI).[5,6] Furthermore, epidemiological data confirm a significant increase in the detection rates of "pituitary incidentalomas" over the years, the majority of which are NFPAs.[7–9] Indeed, in a US population study, incidental detection of pituitary tumours has risen nearly 3-fold between 2004 and 2018.[9] Similarly, in Northern Finland, the standardised incidence rates of pituitary incidentalomas have increased from 0.59 to 1.6 per 100 000 population from years 1992-1999 to 2000-2007, and around half of the total NFPAs were detected incidentally.[8]

Despite these rising trends, the optimal approach to the investigation and management of incidentally detected (presumed) micro-NFPAs remains debated; this was recently highlighted by a UK study that demonstrated considerable variation in the reported clinician approaches to these tumours when surveyed in 2021-2022.[10] Uncertainty regarding the optimal length and frequency of biochemical and imaging surveillance for micro-NFPAs is shaped by a paucity of robust evidence on their natural history, and by the variability in the behaviour of these tumours described by studies to date. Indeed, reported rates of micro-NFPA growth and hypopituitarism range between 0% and 53%,[11–22] and 0% and 50%,[11–22] respectively. Such variations result from limitations in study design and methodology, including small sample size, the inclusion of patients with differing pathology (eg, functioning pituitary adenomas or Rathke's cleft cysts), or different diagnostic approaches for hypopituitarism.[2,11,12,15–17,22,23] Current uncertainty regarding the potential for tumour growth

(and associated clinical consequences) may promote extensive biochemical and/or imaging surveillance incurring unnecessary burden to both patient and health care providers.

We conducted a UK, multi-centre, retrospective cohort study in an effort to adequately understand the natural history of conservatively managed micro-NFPAs. Our aim was to elucidate tumour behaviour, including the probability of enlargement or shrinkage and of developing hypopituitarism, to generate robust evidence to underpin the cost-effective and safe care delivered to this group of patients.

Patients and methods

This was a multi-centre, retrospective, cohort study involving 23 adult endocrine departments (UK NFPA consortium: see Acknowledgments).

Records of patients with the diagnosis of micro-NFPA followed-up in the participating centres between January, 1, 2008 and December, 21, 2021 were reviewed, and clinical, pituitary imaging, and hormonal data at presentation and during monitoring were collected. The cases were identified from the databases of each centre. Diagnosis of micro-NFPA relied on the presence of a pituitary mass with imaging features consistent with an adenoma and maximum diameter <1 cm, and absence of clinical and/or biochemical evidence of hormone hypersecretion. Cystic lesions considered to represent Rathke's cleft cysts were excluded. The frequency of assessment for hypopituitarism and of follow-up scanning was determined by the individual clinician based on their preference/local protocols and/or the clinical picture of the patient.

Secondary hypoadrenalism was confirmed by dynamic testing (either short Synacthen, insulin tolerance, or glucagon test according to local protocols); secondary hypogonadism was defined as low, or inappropriately normal levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) coupled with a morning testosterone below the reference range in males or low oestradiol and oligo/amenorrhoea in women of reproductive age or as gonadotropins below the age reference in post-menopausal women; secondary hypothyroidism was defined as low, or inappropriately normal thyroid-stimulating hormone (TSH) paired with free thyroxine below the reference range. Evaluation for growth hormone (GH) deficiency was not routinely performed in this group of patients, given the specific criteria set by the UK National Institute of Clinical Excellence (NICE) for obtaining GH replacement.[24] For patients diagnosed with pituitary hormone deficits, medical and drug history were reviewed in detail to identify potential confounding factors [eg, opiates/opioids use, severe obesity, exogenous steroid use, low body mass index (BMI), and acute illness]. Tumour size was defined by the largest diameter on MRI at micro-NFPA detection and was compared to tumour sizes reported in subsequent MRIs. Total follow-up duration was defined by date of MRI, beginning at date of tumour detection until date of last available image. In the cases of surgical intervention, date of last available image performed during conservative management was used.

The study was retrospective in nature, and there was no intervention beyond routine delivery of patient care; it was registered with and approved as a clinical audit by the respective departments and there were patient consent waivers. Anonymised data were collected using a standardised proforma. The audit reference number for the co-ordinating centre was CARMS (Clinical Audit Registration and Management System) 16842 (University Hospitals Birmingham NHS Foundation Trust). The research complied with the Declaration of Helsinki.

Statistical analysis

Percentages were estimated for categorical data and medians with IQRs for continuous variables. Comparisons of continuous variables were performed by the Mann–Whitney U-test. Micro-NFPA growth- and reduction-free curves were generated by the Kaplan–Meier method, and the differences between outcomes in subgroups were explored by the log-rank test. Cox regression analysis was used to assess the effect of various factors on tumour growth and hazard ratios with 95% CIs were calculated. There was no significant departure from proportional hazards assumptions for any of the variables. The level of significance was set at $P < .05$. Statistical analyses were performed by IBM SPSS Statistics for Windows, Version 20 (IBM Corp., Armonk, NY, USA).

Results

Patient and micro-NFPA characteristics at presentation

Data for 459 patients with micro-NFPA detected on MRI were retrieved. Median age at tumour identification was 44 years (IQR 31-57); 152 (33.1%) were males and 307 (66.9%) females, with females presenting at an earlier age than males (Table 1). The indications for imaging leading to micro-NFPA detection are shown in Table 2, with the most common being headaches (19.8%). The median maximum diameter of the tumour was 6 mm (IQR 4-8 mm).

Imaging outcomes during follow-up

In total, 419 patients had at least 2 MRIs. The median imaging monitoring period was 3.5 years (IQR 1.7-6.1 years). During this interval, acute pituitary apoplexy was diagnosed in one patient (0.2%) (female with an initial 7 mm micro-NFPA, with apoplexy presenting 16 months later and managed conservatively). Amongst the remaining 418 patients, in 49

Table 1. Patient demographics and tumour characteristics.

Parameters	Values
Age (years), median, (IQR)	44 (31-57)
Age (years), median (IQR), males[a]	48 (38-61)
Age (years), median (IQR), females[a]	36 (30-55)
Sex	
Males	152/459 (33.1%)
Females	307/459 (66.9%)
Size of micro-NFPA at detection (mm), median, (IQR)[b]	6 (4-8)
Micro-NFPAs with maximum diameter <5 mm	125/426 (29.3%)
Micro-NFPAs with maximum diameter ≥5 mm	301/426 (70.7%)
Imaging follow-up duration (years), median, (IQR)[c]	3.5 (1.7-6.1)
Number of MRIs performed in those with imaging follow-up, median, (IQR)[c]	3 (2-4)

Abbreviations: IQR, interquartile range; micro-NFPA, non-functioning pituitary microadenoma; MRI, magnetic resonance imaging; mm, millimetres.
[a]$P < .001$.
[b]Data available for 426 patients.
[c]Data available for 419 patients.

(11.7%) the micro-NFPA enlarged, in 79 (18.9%) it reduced in size, and in 290 (69.4%) it remained stable (Figure 1).

Cumulative probability of tumour growth was 7.8% (95% CI, 4.9%-8.1%), 14.5% (95% CI, 10.2%-18.8%) and 18.3% (95% CI, 13.0%-23.6%) at 3, 5 and 7 years, respectively (Figures 2 and 3, Table 3). Growth incidence was 2.7 (95% CI, 2.0-3.5) per 100 person-years and where maximal tumour diameter data were provided ($n = 41$), median increase was 2 mm (IQR 1-3). Median time until detection of first growth was 3 years (IQR 1.6-4.5) and a median number of three MRIs (range 2-6) were performed prior to this. Twenty-four (49%) of micro-NFPAs that grew became macroadenomas (23 of them were >5 mm at first detection; in the patient with a starting tumour of <5 mm, growth occurred during pregnancy with subsequent reduction in size). In the group of 49 cases with tumour enlargement, 5 were operated on, 18 had no further radiological follow-up available and 26 had imaging monitoring for a median period of 2.1 years (1.3-3.8); in the last subgroup, 12 (48%) showed a further increase in tumour size.

During the whole monitoring period, eight patients with grown adenomas (first episode or after further increase) were managed by surgery (all had become macroadenomas, 1.9% of total cases). During the first 3 years of follow-up, one patient had transsphenoidal surgery [size at detection 9 mm—21 months later, size 17 mm (optic chiasm clear)—operated due to growth]. Reasons for surgical intervention included development of visual field defects secondary to optic chiasm compression ($n = 1$), tumour abutting the optic chiasm but without visual deficit on neuro-ophthalmic assessment ($n = 2$), a wish for pregnancy ($n = 1$), or because of tumour growth alone ($n = 4$). Pathology showed pituitary adenoma ($n = 6$), "areas of necrosis and inflammation" ($n = 1$), or was unavailable ($n = 1$).

Cumulative probability of tumour shrinkage was 14.1% (95% CI, 10.4%-17.8%), 21.3% (95% CI, 16.4%-26.2%), and 26.0% (95% CI, 20.1%-31.9%) at 3, 5 and 7 years, respectively (Figures 4 and 5, Table 3). In the group of 79 cases with tumour shrinkage, 53 had no further follow-up available and 26 had imaging monitoring for a median of 2.1 years (IQR 1.7-3.5); in the last subgroup, 9 (34.6%) had a further reduction (1 of these cases showed gradual reduction over a period of 5 years followed by increase in size in the latest scan 2 years later).

Age at micro-NFPA detection, sex, and size of micro-NFPA at time of detection (maximum diameter or size <5 or ≥5 mm) were not predictors of enlargement or shrinkage (Table 4).

Table 2. Indication for imaging which led to micro-NFPA detection.

Primary indication for imaging	Number of patients (%)
Headache	91 (19.8)
Neurological manifestations (excluding headache)	69 (15.0)
"Incidental" finding with no further details available	67 (14.6)
Hypogonadism	60 (13.1)
Hyperprolactinaemia (proved to be transient)	43 (9.4)
Visual disturbance	20 (4.4)
ENT problems[a]	20 (4.4)
Oligo-/amenorrhea	16 (3.5)
Abnormal thyroid function tests	15 (3.3)
Screening[b]	12 (2.6)
Unknown	12 (2.6)
Galactorrhoea	11 (2.4)
Head injury	5 (1.1)
Hypoadrenalism	4 (0.9)
Hypopituitarism, not further specified	4 (0.9)
Pubertal delay/precocious puberty/short stature	3 (0.7)
Investigation for polyuria/polydipsia	2 (0.4)
Suspected Cushing's syndrome	2 (0.4)
Suspected acromegaly	1 (0.2)
Hyponatraemia	1 (0.2)
Obstructive sleep apnoea	1 (0.2)

Abbreviation: ENT, ear, nose, and throat.
[a]Tinnitus, anosmia, vertigo, otalgia, deafness, sinus or nasal septum or epiglottic problems, and during vestibular schwannoma surveillance.
[b]For patients with Multiple Endocrine Neoplasia 1 or with a history of cancer or of infiltrative/inflammatory disease.

Pituitary function

At baseline, 33 (7.2%), 8 (1.7%), and 7 (1.5%) patients were reported to have secondary hypogonadism, hypothyroidism, and hypoadrenalism (without other documented factors associated with these findings), respectively (Table 5). Forty-one (85.4%) of those with pituitary hormone deficits had tumours ≥5 mm; the remaining seven (14.6%) had isolated hypogonadotropic hypogonadism and their tumour was <5 mm.

During follow-up, repeat assessment of the FSH/LH, TSH, and ACTH axes was performed in 325 (70.8%), 354 (77.0%), and 310 (67.5%) of patients, respectively. Two patients (0.6%) were diagnosed with new hypopituitarism during follow-up: secondary hypothyroidism in one (who already had hypogonadism and hypoadrenalism at baseline), and secondary hypogonadism, hypothyroidism, and hypoadrenalism in the other. In both patients, hypopituitarism was detected after tumour growth (both became macroadenomas).

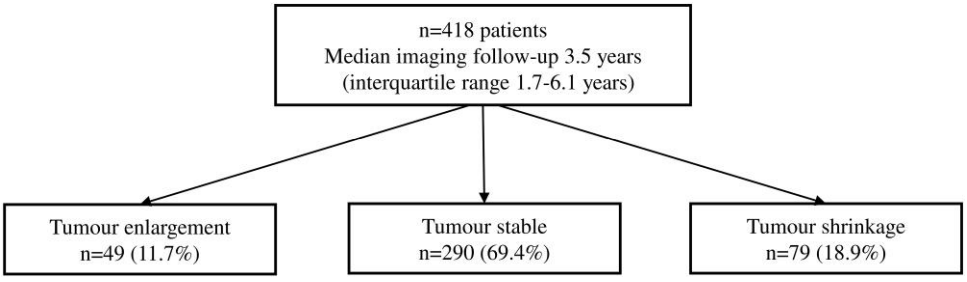

Figure 1. Summary of the outcomes of patients with non-functioning pituitary microadenoma during follow-up ($n = 418$, one patient who developed pituitary apoplexy has been excluded).

Discussion

To our knowledge, this is the largest study to date elucidating the outcomes of presumed micro-NFPAs in 23 participating endocrine departments (UK NFPA consortium). We have shown cumulative probability of tumour growth of 7.8% and 14.5%, at 3 and 5 years, respectively. The growth incidence was 2.7 per 100 person-years with only 1.9% of the total cases undergoing pituitary surgery during the follow-up period. Tumour size, age at micro-NFPA detection, and sex were not predictors of enlargement. Notably, extremely rare events were the diagnosis of new hypopituitarism (reported in only two patients, both of whom had tumour growth) and the development of acute pituitary apoplexy (in just one patient with an initial tumour size of 7 mm).

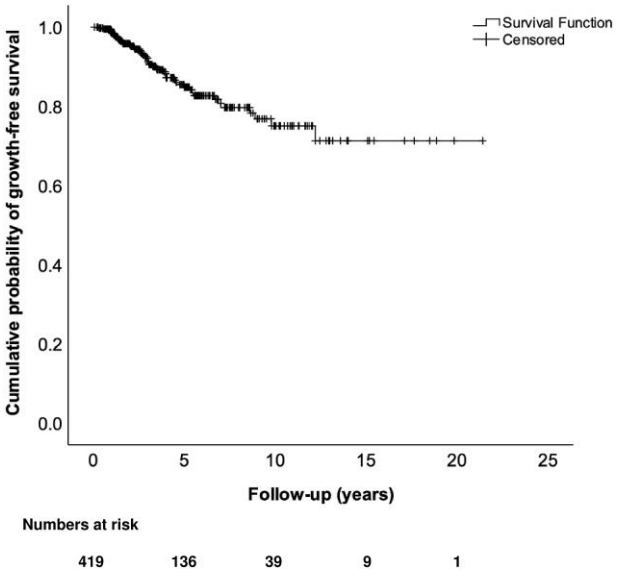

Figure 2. Cumulative probability of non-functioning pituitary microadenoma growth-free survival.

Our results on tumour enlargement based on the monitoring of 419 cases are in accord with the findings of some,[12,14,25] but not all[16,23] studies. In a cohort of presumed micro-NFPAs followed for a mean period of 41 months, growth was reported in 12.5%, with cumulative probability of enlargement of 19% at 4 years.[12] In a series of 271 patients with micro-NFPAs monitored for a median period of 29 months, growth was documented in 8.1% of cases [growth incidence 2.1 per 100 person-years (95% CI, 1.4-3.3)].[14] By contrast, in one study with 19 micro-NFPAs, growth was reported in 52.6% over a median follow-up of 3.9 years (observation period was provided for both macro- and micro-NFPAs).[16] Disparity between our findings and this study may be explained by the considerable difference in cohort sizes. In a series of 177 patients with a pituitary tumour ≤10 mm and monitored by MRI for a median period of 4.9 years, increase in size was reported in 28%, with overall slow growth rates; amongst the small number of cases undergoing tumour resection, a majority proved to be functioning

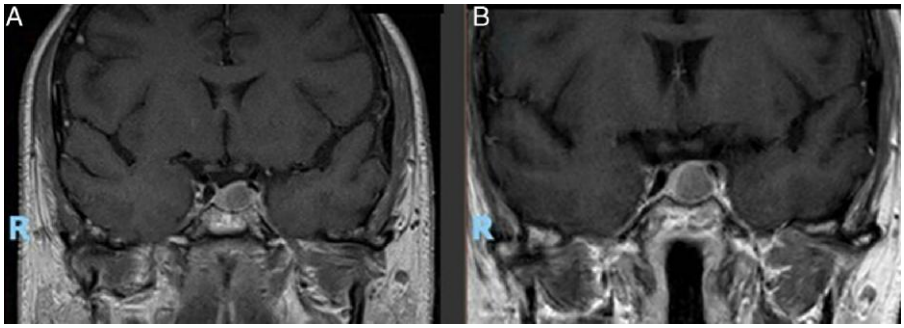

Figure 3. (A) Baseline sagittal, post-contrast T1-weighted MRI demonstrating an 8.6 mm presumed NFPA in the left side of the sella. (B) Sagittal, post-contrast T1-weighted MRI demonstrating enlargement of the tumour 4 years after the baseline imaging (macroadenoma, 12 mm).

Table 3. Cumulative probability of tumour growth and reduction.

	Total	<5 mm[a]	≥5 mm[a]
Cumulative probability of tumour growth (95% CI)			
1 year	1.3% (0.1-1.9)	0%	1.9% (0.3-3.5)
2 years	4.2% (2.0-6.4)	1.1% (0.0-3.3)	5.7% (2.8-8.6)
3 years	7.8% (4.9-8.1)	4.6% (0.0-9.9)	9.9% (8.0-11.8)
5 years	14.5% (10.2-18.8)	13.9% (3.7-24.1)	15.4% (10.1-20.7)
7 years	18.3% (13.0-23.6)	13.9% (3.7-24.1)	19.6% (13.1-26.1)
	Total	**<5 mm[b]**	**≥5 mm[b]**
Cumulative probability of tumour reduction (95% CI)			
1 year	3.0% (1.2-4.8)	4.7% (0.8-8.6)	2.3% (0.5-4.1)
2 years	9.6% (6.5-11.2)	9.4% (3.5-15.3)	10.2% (6.5-13.9)
3 years	14.1% (10.4-17.8)	15.4% (7.4-23.4)	14.8% (10.1-18.6)
5 years	21.3% (16.4-26.2)	28.8% (17.4-40.2)	20.6% (14.9-26.3)
7 years	26.0% (20.1-31.9)	36.0% (21.9-50.1)	25.3% (18.2-32.4)

[a]Log rank $P = .77$.
[b]Log rank $P = .45$.

pituitary adenomas or Rathke's cleft cyst and the authors acknowledged that they did not perform subgroup analysis on cystic and solid lesions.[26] In our study, the cumulative probability of tumour reduction was 14.1% at 3 years with a speculative mechanism being ischaemic changes within the tumour.

Currently, for all micro-NFPAs, the Endocrine Society recommends MRI 1 year after detection, and if stable, every 1-2 years for 3 years, and less often thereafter.[27] Similarly, the German Society for Endocrinology recommends annual MRI for 3 years, and if no change in tumour size, subsequent imaging is organised based on individual evaluation and discussion with the patient.[28] Others do not recommend further imaging surveillance for micro-NFPAs smaller than 5 mm at detection.[29,30] In a UK survey between 2021 and 2022, there was significant heterogeneity in the imaging monitoring practice adopted amongst clinicians.[10] Interestingly 31% would perform pituitary MRI at 1 year, 18.3% at 1 and 2 years and 18.3% at 1, 2, and 3 years; in all approaches, the patient would be discharged if there was tumour stability.[10] Our data challenge this approach and the existing guidelines, as the median increase during the whole follow-up period in the group of tumours that enlarged was only 2 mm (IQR 1-3) and the probability of tumour growth in the first 3 years was low. Furthermore, only one patient was offered surgery during the first 3 years of monitoring (due to tumour growth rather than impact on the optic pathways). Consequently, extending the initial imaging interval to 3 years after micro-NFPA detection appears to be a safe, and arguably a more cost-effective approach to micro-NFPA surveillance.

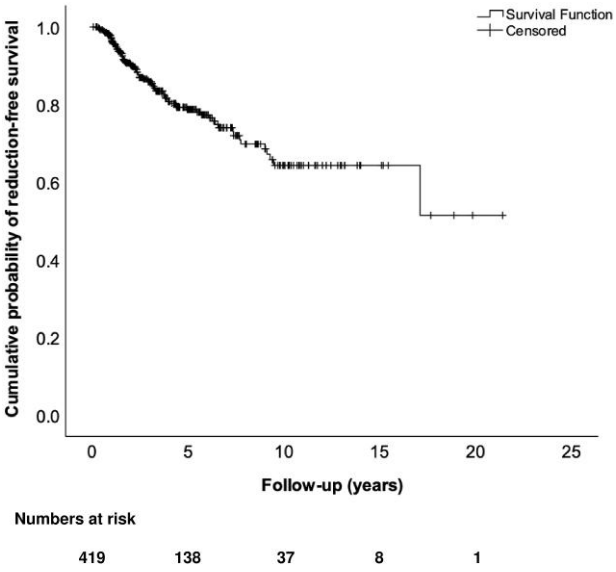

Figure 4. Cumulative probability of non-functioning pituitary microadenoma reduction-free survival.

We did not identify clinical predictors of tumour enlargement, particularly tumour size. It is of interest that there was a trend for older age to be associated with higher risk of micro-NFPA growth; larger studies would help clarify whether this is a true finding. In ours, as well as in other studies,[14,25,31] the relatively short duration of follow-up has not allowed the establishment of the optimal timing for patient discharge. This short monitoring interval reflects real-world data, as most clinicians discharge the patients within 3 years of confirming tumour stability.[10] Given the small-scale median increase in tumour size (also supported by others[26]), it could be argued that elderly patients and particularly those with tumours <5 mm could be safely discharged after interval

Table 4. Hazard ratios for micro-NFPA growth and reduction.

Variable	Tumour growth Hazard ratio, 95% CI, *P* value	Tumour reduction Hazard ratio, 95% CI, *P* value
Age at micro-NFPA detection	1.02 per year 1.00-1.04 .06	1.00 per year 0.99-1.02 .58
Sex	0.64 0.36-1.21 .12	1.19 0.72-1.96 .49
Tumour size (maximum diameter in mm)	1.09 0.94-1.26 .26	0.98 0.88-1.10 .68
Tumour size (<5 or ≥5 mm)	1.79 0.80-4.00 .16	0.83 0.50-1.36 .45

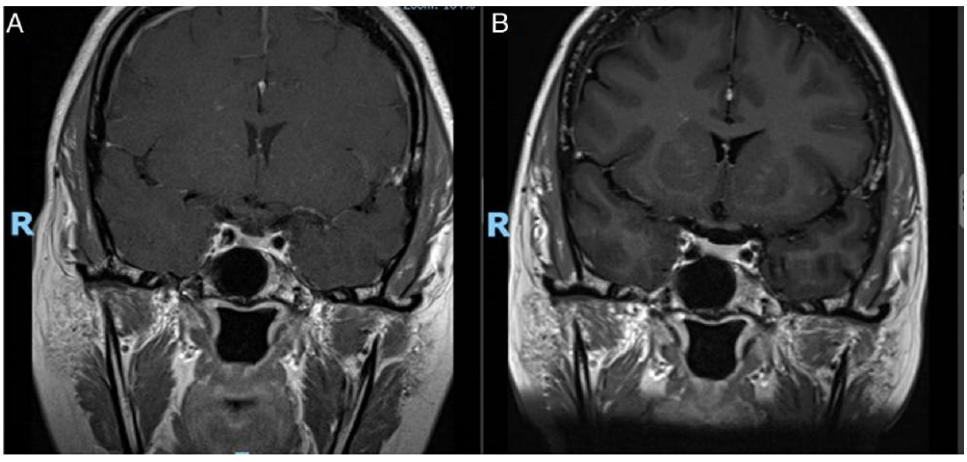

Figure 5. (A) Baseline sagittal, post-contrast T1-weighted MRI demonstrating a 3.5 mm presumed NFPA in the right side of the sella. (B) Sagittal, post-contrast T1-weighted MRI demonstrating shrinkage of the tumour 1 year after the baseline imaging.

Table 5. Prevalence of reported pituitary hormone deficits at time of micro-NFPA detection.

Pituitary hormone deficiency	Number of patients (%)
Isolated FSH/LH deficiency	26 (5.7)
Isolated TSH deficiency	3 (0.7)
Isolated ACTH deficiency	1 (0.2)
FSH/LH and TSH deficiency	1 (0.2)
FSH/LH and ACTH deficiency	2 (0.4)
FSH/LH, TSH and ACTH deficiency	4 (0.9)

Abbreviations: ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinising hormone; TSH, thyroid-stimulating hormone.

imaging at 3 years, or even at the time of the micro-NFPA detection. This would be after discussion with the patient explaining the rationale of this approach. During a median imaging follow-up period of 3.5 years, 1.9% of our cases were offered surgery with only three out of eight compressing or abutting the optic pathway. Whether a longer observation interval could result in a larger ratio of clinically significant tumour enlargement remains to be clarified. In a small subset of tumours that increased in size, growth continued; clarification of the clinical significance of this trend would require longer-term surveillance.

The most frequent indication for imaging leading to tumour detection was headache (20% of cases), a symptom commonly reported in this group of patients.[14,17,32] Whether the micro-NFPA is indeed responsible for the headaches is difficult to establish, particularly for smaller lesions that do not trigger pain through dural tears or cavernous sinus invasion.[33]

After micro-NFPA detection, a minority of patients were found with pituitary hormone deficits at baseline; 7.2% with secondary hypogonadism, 1.7% with secondary hypothyroidism, and 1.5% with secondary hypoadrenalism. Interestingly, in 15% of the cases, the tumour size was <5 mm. Whether the aetiology of the pituitary dysfunction correlates with pressure effects from the micro-NFPA in all cases is not clear and this could be particularly debated for small tumours or in the cases of reported isolated ACTH or TSH deficiency. Our results are in concordance with other series,[14,17,20,21,34] though exceptions include one study with loss of at least two hormonal axes in 50%,[18] and another with loss of one or more hormonal axes (most commonly LH/FSH and TSH deficiencies) in 42% of cases with micro-NFPAs.[16] It should be highlighted that both studies had a small sample size (19 and 38 patients),[16,18] and the possibility of clinical confounders in the patient groups cannot be excluded (eg, in the study with a 50% rate of hypopituitarism, patients' mean BMI was 36.2 kg/m^2).[18] In our cohort, a considerable number of patients were screened for hypopituitarism in the absence of known tumour growth. This also featured in the UK survey, in which 47% of the respondents opted for annual pituitary function assessment.[10] We found that only 0.6% of the patients developed new hypopituitarism (detected after tumour growth which became macroadenoma). Our findings (also supported by the results of others[14,25,35]), underpin the concept that there is little value in repeated hormonal screening in patients with stable imaging or no new clinical manifestations of hypopituitarism, as recommended by the Endocrine Society[27] and the French Society of Endocrinology guidelines.[30]

Strengths of this study include its large sample size and its multi-centre design with wide representation of UK endocrine departments, allowing the inclusion of more diverse groups of patients. Furthermore, those with hypopituitarism—either at baseline or diagnosed during follow-up—were carefully screened to clarify whether the hormonal deficits could be attributable to other confounding factors. Limitations include the lack of pathological confirmation of the diagnosis of adenoma which is, however, inherent to this study that aimed to investigate the outcomes of conservatively managed presumed micro-NFPAs. Variation in image interpretation amongst radiologists from participating centres needs to be considered and this could not be ameliorated due to the retrospective nature of the study; nonetheless, the findings represent "real-world" data reflecting daily clinical practice. GH deficiency was not routinely evaluated given the specific criteria for obtaining GH replacement set by the UK healthcare funding regulator (NICE). The long interval covering this study, the wide geographical and organisational spread of the participating departments, as well as the variations and changes in the reporting practices may have introduced under-reporting of the micro-NFPAs in the databases of the centres. Finally, similarly to previous studies,[12,14,16] the follow-up duration did not allow us to provide estimates of tumour behaviour in the longer term.

The findings for this large, multi-centre study have further elucidated uncertainties over the natural history of conservatively managed micro-NFPAs and inform clinical practice. The low probability of tumour growth, especially during the first 3 years from micro-NFPA detection, combined with the absence of relevant clinical consequences, provides reassurance for both clinicians and patients. They also give ground to the argument for revising the current international imaging recommendations, as it has also been proposed in two smaller single-institution US reports.[14,26] Delaying the first follow-up MRI to 3 years and reinforcing the need to avoid re-evaluation of pituitary function in the absence of tumour growth or of relevant clinical manifestations are important cost-effective approaches and, given the expanding detection rates of micro-NFPAs, could lead to considerable financial savings and spare significant resources for healthcare systems. In the absence of predictors of micro-NFPA growth, defining the group of patients requiring closer attention is challenging. Until longer-term follow-up studies are available, imaging at 3 years and if the tumour is stable, at 6 years from time of micro-NFPA detection would be a reasonable approach with an earlier scan dictated by a high index of suspicion of growth (eg, visual field deficits) or clinical signs of apoplexy.

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References

1. Rogers A, Karavitaki N, Wass JA. Diagnosis and management of prolactinomas and non-functioning pituitary adenomas. *BMJ*. 2014;349:g5390. https://doi.org/10.1136/bmj.g5390
2. Fernandez A, Karavitaki N, Wass JA. Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). *Clin Endocrinol (Oxf)*. 2010;72(3):377-382. https://doi.org/10.1111/j.1365-2265.2009.03667.x
3. Ntali G, Wass JA. Epidemiology, clinical presentation and diagnosis of non-functioning pituitary adenomas. *Pituitary*. 2018;21(2):111-118. https://doi.org/10.1007/s11102-018-0869-3
4. Molitch ME. Pituitary incidentalomas. *Best Pract Res Clin Endocrinol Metab*. 2009;23(5):667-675. https://doi.org/10.1016/j.beem.2009.05.001
5. Hall WA, Luciano MG, Doppman JL, Patronas NJ, Oldfield EH. Pituitary magnetic resonance imaging in normal human volunteers: occult adenomas in the general population. *Ann Intern Med*. 1994;120(10):817-820. https://doi.org/10.7326/0003-4819-120-10-199405150-00001
6. Chong BW, Kucharczyk W, Singer W, George S. Pituitary gland MR: a comparative study of healthy volunteers and patients with microadenomas. *AJNR Am J Neuroradiol*. 1994;15(4):675-679.
7. Agustsson TT, Baldvinsdottir T, Jonasson JG, *et al*. The epidemiology of pituitary adenomas in Iceland, 1955-2012: a nationwide population-based study. *Eur J Endocrinol*. 2015;173(5):655-664. https://doi.org/10.1530/EJE-15-0189
8. Raappana A, Koivukangas J, Ebeling T, Pirilä T. Incidence of pituitary adenomas in Northern Finland in 1992-2007. *J Clin Endocrinol Metab*. 2010;95(9):4268-4275. https://doi.org/10.1210/jc.2010-0537
9. Watanabe G, Choi SY, Adamson DC. Pituitary incidentalomas in the United States: a national database estimate. *World Neurosurg*. 2022;158:e843-e855. https://doi.org/10.1016/j.wneu.2021.11.079
10. Hamblin R, Fountas A, Levy M, Karavitaki N. UK Practice on incidentally detected non-functioning pituitary microadenomas: analysis of two national surveys during a 12-year interval. *Pituitary*. 2023;26(1):94-104. https://doi.org/10.1007/s11102-022-01290-4
11. Donovan LE, Corenblum B. The natural history of the pituitary incidentaloma. *Arch Intern Med*. 1995;155(2):181-183. https://doi.org/10.1001/archinte.1995.00430020067008
12. Karavitaki N, Collison K, Halliday J, *et al*. What is the natural history of nonoperated nonfunctioning pituitary adenomas? *Clin Endocrinol (Oxf)*. 2007;67(6):938-943. https://doi.org/10.1111/j.1365-2265.2007.02990.x
13. Feldkamp J, Santen R, Harms E, Aulich A, Mödder U, Scherbaum WA. Incidentally discovered pituitary lesions: high frequency of macroadenomas and hormone-secreting adenomas—results of a prospective study. *Clin Endocrinol (Oxf)*. 1999;51(1):109-113. https://doi.org/10.1046/j.1365-2265.1999.00748.x
14. Han AJ, Varlamov EV, Fleseriu M. Nonfunctioning pituitary microadenomas: should imaging interval be extended? A large single-center cohort study. *J Clin Endocrinol Metab*. 2022;107(3):e1231-e1241. https://doi.org/10.1210/clinem/dgab748
15. Reincke M, Allolio B, Saeger W, Menzel J, Winkelmann W. The 'incidentaloma' of the pituitary gland. Is neurosurgery required? *JAMA*. 1990;263(20):2772-2776. https://doi.org/10.1001/jama.1990.03440200076026
16. Sam AH, Shah S, Saleh K, *et al*. Clinical outcomes in patients with nonfunctioning pituitary adenomas managed conservatively. *Clin Endocrinol (Oxf)*. 2015;83(6):861-865. https://doi.org/10.1111/cen.12860
17. Sanno N, Oyama K, Tahara S, Teramoto A, Kato Y. A survey of pituitary incidentaloma in Japan. *Eur J Endocrinol*. 2003;149(2):123-127. https://doi.org/10.1530/eje.0.1490123
18. Yuen KC, Cook DM, Sahasranam P, *et al*. Prevalence of GH and other anterior pituitary hormone deficiencies in adults with nonsecreting pituitary microadenomas and normal serum IGF-1 levels. *Clin Endocrinol (Oxf)*. 2008;69(2):292-298. https://doi.org/10.1111/j.1365-2265.2008.03201.x
19. Tresoldi AS, Carosi G, Betella N, *et al*. Clinically nonfunctioning pituitary incidentalomas: characteristics and natural history. *Neuroendocrinology*. 2020;110(7-8):595-603. https://doi.org/10.1159/000503256
20. Kim JH, Dho Y-S, Kim YH, *et al*. Developing an optimal follow-up strategy based on the natural history of nonfunctioning pituitary adenomas. *J Neurosurg*. 2019;131(2):500-506. https://doi.org/10.3171/2018.4.JNS172148
21. Lenders N, Ikeuchi S, Russell AW, Ho KK, Prins JB, Inder WJ. Longitudinal evaluation of the natural history of conservatively managed nonfunctioning pituitary adenomas. *Clin Endocrinol (Oxf)*. 2016;84(2):222-228. https://doi.org/10.1111/cen.12879
22. Anagnostis P, Adamidou F, Polyzos SA, Efstathiadou Z, Panagiotou A, Kita M. Pituitary incidentalomas: a single-centre experience. *Int J Clin Pract*. 2011;65(2):172-177. https://doi.org/10.1111/j.1742-1241.2010.02537.x
23. Arita K, Tominaga A, Sugiyama K, *et al*. Natural course of incidentally found nonfunctioning pituitary adenoma, with special reference to pituitary apoplexy during follow-up examination. *J Neurosurg*. 2006;104(6):884-891. https://doi.org/10.3171/jns.2006.104.6.884

24. National Institute for Health and Care Excellence. Human growth hormone (somatropin) in adults with growth hormone deficiency [Technology appraisal guidance [TA64]]. 2003. https://www.nice.org.uk/guidance/ta64
25. Fernández-Balsells MM, Murad MH, Barwise A, *et al.* Natural history of nonfunctioning pituitary adenomas and incidentalomas: a systematic review and metaanalysis. *J Clin Endocrinol Metab*. 2011;96(4):905-912. https://doi.org/10.1210/jc.2010-1054
26. Hordejuk D, Cheung Y-MM, Wang W, *et al.* Long-term changes in the size of pituitary microadenomas. *Ann Intern Med*. 2023;176(3):298-302. https://doi.org/10.7326/M22-1728
27. Freda PU, Beckers AM, Katznelson L, *et al.* Pituitary incidentaloma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(4):894-904. https://doi.org/10.1210/jc.2010-1048
28. Deutschbein T, Jaursch-Hancke C, Knappe UJ, *et al.* First German guideline on diagnostics and therapy of clinically non-functioning pituitary tumors. *Exp Clin Endocrinol Diabetes*. 2021;129(3):250-264. https://doi.org/10.1055/a-1373-4087
29. Boguszewski CL, de Castro Musolino NR, Kasuki L. Management of pituitary incidentaloma. *Best Pract Res Clin Endocrinol Metab*. 2019;33(2):101268. https://doi.org/10.1016/j.beem.2019.04.002
30. Galland F, Vantyghem M-C, Cazabat L, *et al.* Management of non-functioning pituitary incidentaloma. *Ann Endocrinol (Paris)*. 2015;76(3):191-200. https://doi.org/10.1016/j.ando.2015.04.004
31. Pernik MN, Montgomery EY, Isa S, *et al.* The natural history of non-functioning pituitary adenomas: a meta-analysis of conservatively managed tumors. *J Clin Neurosci*. 2022;95:134-141. https://doi.org/10.1016/j.jocn.2021.12.003
32. Constantinescu SM, Maiter D. Pituitary incidentaloma. *Presse Med*. 2021;50(4):104081. https://doi.org/10.1016/j.lpm.2021.104081
33. Kreitschmann-Andermahr I, Siegel S, Weber Carneiro R, Maubach JM, Harbeck B, Brabant G. Headache and pituitary disease: a systematic review. *Clin Endocrinol (Oxf)*. 2013;79(6):760-769. https://doi.org/10.1111/cen.12314
34. Al Argan R, Ramadhan A, Agnihotram RV, Chankowsky J, Rivera J. Baseline MRI findings as predictors of hypopituitarism in patients with non-functioning pituitary adenomas. *Endocr Connect*. 2021;10(11):1445-1454. https://doi.org/10.1530/EC-21-0386
35. Imran SA, Yip C-E, Papneja N, *et al.* Analysis and natural history of pituitary incidentalomas. *Eur J Endocrinol*. 2016;175(1):1-9. https://doi.org/10.1530/EJE-16-0041