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Original Research

Conservatively managed non-functioning pituitary macroadenomas—cohort study from the UK Non-functioning Pituitary Adenoma Consortium

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Abstract

Objective: Surveillance is often adopted for asymptomatic non-functioning pituitary macroadenomas (macroNFPAs). Due to low-quality evidence, uncertainty remains on optimal frequency of imaging/biochemical monitoring and indications for surgery. We assessed the natural history and outcomes of patients with macroNFPA who had monitoring as initial management choice from the UK NFPA Consortium.

Design: This was a multicentre, retrospective, cohort study involving 21 UK endocrine departments.

Methods: Clinical, imaging, and hormonal data of 949 patients followed up between January, 1, 2005 and March, 1, 2022 were analysed.

Results: Incidence rate for tumour enlargement was 9.8 per 100 patient-years (95% CI, 8.8-10.8), with cumulative probabilities 1.6%, 8.1%, 18.4%, 29.2%, and 43.6% at 6-month, 1-year, 2-year, 3-year, and 5-year follow-up, respectively; rates were higher in tumours abutting/displacing optic chiasm than those not in contact with it. Amongst macroNFPAs not in contact with optic chiasm showing enlargement within 6 months, none impacted visual fields. In tumours with enlargement and continued monitoring (median 2.6 years), further growth occurred in 60.5% (33.8% probability at 2 years), stability in 35.5%, and shrinkage in 4.0%. Rates of new pituitary hormone deficits were 4.0%-4.9%, mainly driven by tumour enlargement. After transsphenoidal surgery, rates of hypopituitarism reversal were 12%-17% and those of additional anterior pituitary hormone deficits were 12%-15% (permanent vasopressin deficiency 3.5%).

Conclusions: Our data provide evidence for monitoring protocols. MacroNFPAs not in contact with optic chiasm require less frequent imaging, and first follow-up scan can be delayed to 1 year. After first enlargement, variable tumour behaviour can occur. New hypopituitarism in stable tumours is rare, challenging necessity of regular pituitary function assessment.

Keywords: non-functioning, pituitary, adenoma, PitNET, growth

Significance

To our knowledge, this is the largest study investigating outcomes of patients with non-functioning pituitary macroadenoma initially managed by surveillance and informs clinical practice. Probability of tumour growth increases over time (43.6% at 5 years) and is higher in tumours abutting/displacing optic chiasm compared with those not in contact with it. In tumours not in contact with optic chiasm, probability of growth at 6 months and 1 year was 1.3% and 6.0%, respectively, and follow-up scan can be delayed for around 1 year. After first episode of enlargement, tumours demonstrate variable behaviour. After transsphenoidal surgery, rates of reversal of hypopituitarism were 12%-17% and those of additional anterior pituitary hormone deficits were 12%–15% (permanent diabetes insipidus 3.5%). Development of new hypopituitarism in radiographically stable tumours is rare.

Introduction

Non-functioning pituitary adenomas (NFPAs) are benign adenohypophyseal tumours without clinical evidence of hormonal hypersecretion[1] and the second most common type of pituitary adenomas after prolactinomas.[2,3] Non-functioning pituitary macroadenomas (macroNFPAs) have a prevalence between 12.5 and 28.5 per 100 000 population.[4,5] Non-functioning pituitary macroadenomas can be diagnosed when they are large enough to cause pressure effects to surrounding structures (eg, visual deterioration, hypopituitarism), or are detected incidentally with increasing frequency due to higher availability and utilization of neuroimaging in clinical practice.[6]

Various guidelines/consensus recommend surgery in macroNFPAs causing neuro-ophthalmological manifestations or abutting/compressing the optic chiasm,[7-9] or suggest that this is also considered when there is loss of pituitary function.[7,8] A "watch-and-wait" approach has been advocated in most other cases of asymptomatic macroNFPAs, and various monitoring protocols have been proposed.[7-9] It should be noted, however, that the evidence underpinning several of the proposed points for clinical practice is of low quality and uncertainty remains on the optimal frequency of imaging and biochemical surveillance, as well as on some indications for surgery. Indeed, published literature includes mainly small series of patients from single centres, often with a small number of events carrying risk of imprecise estimates, or cohorts of selected patients not permitting the generation of data sufficient to provide a broad view of the natural history and outcomes of the whole group of conservatively managed macroNFPAs.[10-16] Finally, studies on the behaviour of these tumours after the first episode of growth or shrinkage are lacking.

To overcome these limitations and generate robust data that could underpin clinical practice in this challenging area, we conducted a UK, multicentre, retrospective cohort study including all patients with conservatively managed presumed macroNFPA from the UK NFPA Consortium. Our aim was to elucidate the natural history of this group of tumours, with particular focus on probability of enlargement or shrinkage; factors associated with these; development of pituitary dysfunction; outcomes after surgical intervention; and tumour behaviour after the first episode of growth or shrinkage.

Patients and methods

Study design and participants

We conducted a multicentre, retrospective cohort study on patients with a macroNFPA who had monitoring as initial choice

of management and were followed up between January, 1, 2005 and March, 1, 2022 in 21 adult endocrine centres (UK NFPA Consortium: see acknowledgments). Diagnosis of macroNFPA relied on the presence of pituitary mass with imaging features consistent with macroadenoma, and absence of clinical and/or biochemical evidence of pituitary hormone hypersecretion.[1,17] The cases were identified from the databases of each participating centre. Exclusion criteria were presentation with acute apoplexy at the time of tumour detection, lack of imaging follow-up, and administration of dopamine agonist aiming to control macroNFPA growth. The selection process of the cases is shown in the flowchart in Figure 1. Demographic, clinical, pituitary imaging, hormonal, and visual assessment data at presentation and during monitoring were collected from the patients' records. The frequency of these assessments was determined by the individual clinician/team, based on local protocols and/or patients' clinical picture.

Secondary hypogonadism was defined as low, or inappropriately normal levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) combined with morning testosterone below the reference range in males, or low oestradiol and oligo/amenorrhoea in pre-menopausal women, or as gonadotropins below the age reference in post-menopausal women. Secondary hypoadrenalism was diagnosed based on morning cortisol, or by dynamic testing (either short Synacthen, insulin tolerance, or glucagon test) using local cut-off values for cortisol. Secondary hypothyroidism was defined as low, or inappropriately normal thyroid-stimulating hormone (TSH) paired with free thyroxine levels below the reference range. Assessment for growth hormone (GH) deficiency was not routinely performed, given the specific criteria set by the UK National Institute of Clinical Excellence for obtaining GH replacement.[18] In patients diagnosed with pituitary hormone deficits, medical and drug history was evaluated to exclude potential confounding factors (eg, use of opioids or steroids, acute illness). Visual function evaluation was performed by assessment of visual acuity and visual fields (Goldman or Humphrey perimetry). Reported tumour sizes were compared during serial scans (tumour growth or shrinkage was based on dimension measurements, and it was defined as visible, documented change on any dimension during the imaging surveillance); total imaging monitoring duration was defined by date of scan at tumour detection (time 0) until date of last available image (in the cases offered surgical intervention, date of last available image performed during conservative management was used). Clinical follow-up duration was defined from date of scan at tumour detection (time 0) until date of last clinical contact with the patient or, in those offered pituitary surgery, until date of operation.

The study involved no intervention beyond routine patient care. Institutional approval was obtained from each centre before the contribution of retrospective data, and anonymized data were collected using a specific proforma. Each site has patient consent waivers. The research complied with the Declaration of Helsinki.

Statistical analyses

Percentages were used for categorical variables and medians with ranges for continuous variables. Mann–Whitney U-test

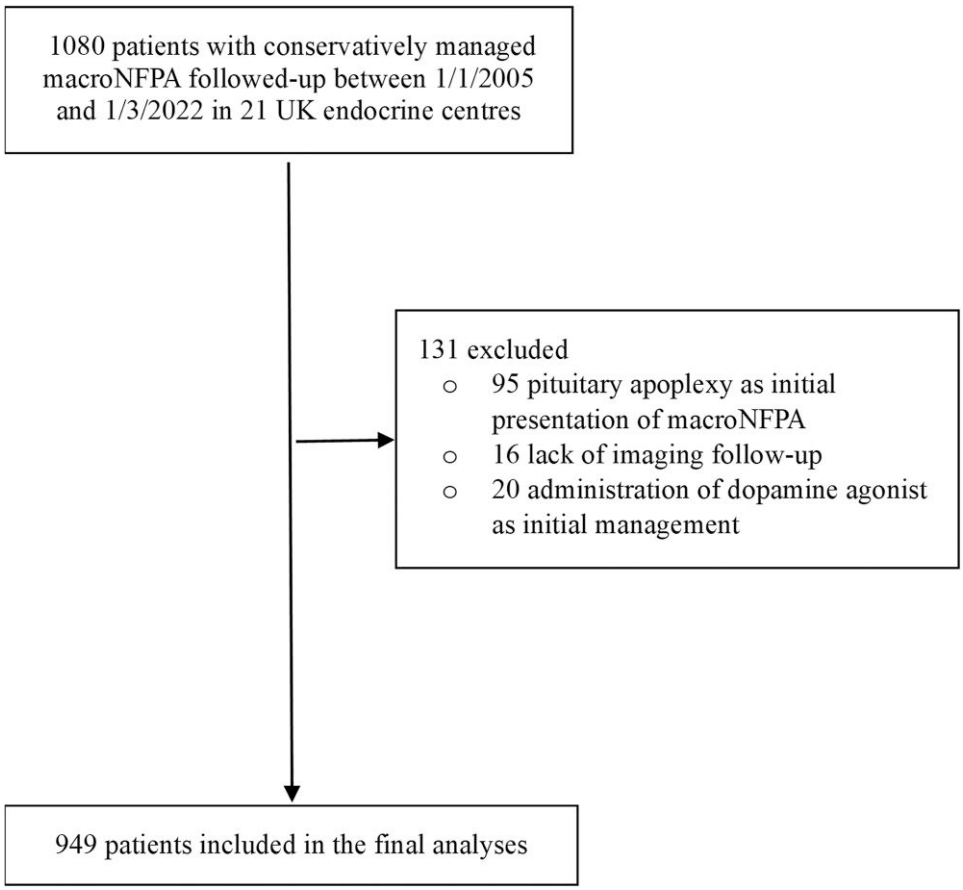

Figure 1. Flowchart showing the cases selection process. macroNFPA, non-functioning pituitary macroadenoma.

was used for comparisons of continuous variables. Tumour growth-free or shrinkage curves were generated by Kaplan–Meier analysis, and differences between groups were assessed by the log-rank test. Univariable and multivariable Cox regression analyses were performed to identify predictors of tumour growth and shrinkage, and hazard ratios (HRs) with 95% CIs were estimated. There was no significant departure from proportional hazards assumptions for the variables. Incidence rates of tumour growth, or pituitary apoplexy during follow-up with 95% CIs were estimated from the number of cases showing tumour growth, or developing pituitary apoplexy, respectively, divided by the amount of person-time at risk (Mid-P exact test). Level of statistical significance was set at $P < .05$. Statistical analyses were conducted with IBM SPSS statistics for Windows (version 29; IBM, Armonk, NY, United States) and by Open Epi (version 3.01).

Results

Patients and macroNFPAs characteristics at presentation

A total of 949 patients were included with a median age of 63 years at macroNFPA detection. Imaging follow-up was performed by magnetic resonance imaging (MRI) (except 4 cases who had CT) with a median duration of 3.6 years (IQR 1.9-6.6). The primary reason for no surgical intervention was absence of visual dysfunction attributed to macroNFPA (84.5% of cases). Demographic, clinical, and imaging data of the patients at the time of macroNFPA detection are given in Table 1.

Table 1. Demographic, clinical, and imaging data of the patients at the time of non-functioning pituitary macroadenoma detection.

Variables	Values
Total number of patients	949
Age at macroNFPA detection (years), median (IQR)	63 (49-75)
Age at macroNFPA detection in males (years), median (IQR)[a]	68 (49-75)[a]
Age at macroNFPA detection in females (years), median (IQR)[a]	54 (49-75)[a]
Sex	
Males (number, %)	549 (57.9%)
Females (number, %)	400 (42.1%)
Maximum diameter of macroNFPA (mm), median (IQR)[b]	17 (13-21)
Presenting manifestations[c]	
Incidentally found	583 (63.2%)
Manifestations of pituitary dysfunction	172 (18.7%)
Headache	107 (11.6%)
Neuro-ophthalmological manifestations	57 (6.2%)
Other	3 (0.3%)
Imaging features	
Only intrasellar (number, %)[d]	143 (15.1%)
Suprasellar (number, %)[d]	526 (55.7%)
Cavernous sinus invasion (number, %)[d]	239 (25.2%)
More than 1 extension (number, %)[d]	233 (24.6%)
Abutting or displacing optic chiasm (number, %)[e]	471 (49.6%)
Purely solid/presence of cystic component or haemorrhage (number, %)[d]	789 (83.6%)/ 155(16.4%)
Pituitary function	
Gonadotropin deficiency (number, %)[f]	301 (33.0%)
ACTH deficiency (number, %)[g]	161 (17.8%)
TSH deficiency (number, %)[h]	196 (21.2%)
Reasons for no surgical intervention for the macroNFPA	
No visual dysfunction attributed to tumour	802 (84.5%)
Comorbidities/poor surgical candidates	70 (7.4%)
Patient's choice	62 (6.5%)
MacroNFPA detected during pregnancy	4 (0.4%)
Unknown	11 (1.2%)
Imaging follow-up (years), median (IQR)	3.6 (1.9-6.6)
Imaging follow-up (patient-years)	4667.8
Number of MRIs performed in those with imaging follow-up, median (IQR)	3 (2-5)
Clinical follow-up (years), median (IQR)	3.8 (2.2-6.8)
Clinical follow-up (patient-years)	4999.5

[a]$P < .001$ for age at macroNFPA detection between males and females. [b]Data available for 894 patients. [c]Data available for 922 patients. [d]Data available for 944 patients. [e]Data available for 943 patients. [f]Data available for 912 patients. [g]Data available for 903 patients. [h]Data available for 926 patients. Abbreviations: macroNFPA, non-functioning pituitary macroadenoma; ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone.

Outcomes during monitoring

During the monitoring period, 385 (40.6%) macroNFPAs increased in size, 481 (50.7%) remained stable, and 83 (8.7%) decreased. Incidence rate for tumour enlargement was 9.8 per 100 patient-years (95% CI, 8.8-10.8). Median time until detection of first growth was 2.4 years (IQR 1.3-4.3). Incidence rate for developing pituitary apoplexy during the clinical follow-up interval was 0.30 per 100 patient-years (95% CI, 0.18-0.49).

Cumulative probability of tumour enlargement in the total group of tumours was 1.6%, 8.1%, 18.4%, 29.2%, and 43.6% at 6-month, 1-year, 2-year, 3-year, and 5-year follow-up, respectively (Figure 2A and Table 2). Probability of macroNFPA enlargement was higher in tumours abutting or displacing the optic chiasm compared with those not in contact with it (Figure 2B and Table 2).

From the group of 472 tumours originally not in contact with the optic chiasm, 179 showed growth during a median interval of 2.7 years (IQR 1.4-4.6), with 83 (17.6%) of them abutting or displacing the optic chiasm. In 6 macroNFPAs, enlargement was detected between 3 and 6 months with none impacting visual fields (1.3% of total group). Deterioration of visual fields was reported in 12 patients [7.1% (data available for 169 cases with growth)]; 11 had surgery leading to normalization of visual fields in 7, improvement in 3, and no change in 1 patient.

From the 301 tumours abutting but not displacing the optic chiasm and not causing visual field defects, 130 showed growth during a median interval of 2.8 years (IQR 1.5-5.0). In 4 macroNFPAs, enlargement was detected between 3 and 6 months with none impacting visual fields (1.3% of total group). Deterioration of visual fields was reported in 35 patients (29.2%, data available for 120 cases with growth); 24 had surgery and based on available information from 21 cases, normalization of visual fields occurred in 12, improvement in 7 and no change in 2 patients. Eight patients were diagnosed with visual field defects without obvious tumour enlargement on imaging; surgery was offered in 3, leading to visual fields improvement in all.

On univariable Cox regression analysis, age at macroNFPA detection, male sex, maximum diameter, cavernous sinus invasion, tumours with extensions beyond the sellar (as compared to only intrasellar ones), tumours with more than 1 extension, and tumours abutting/displacing optic chiasm (as compared to those not in contact with it) were predictors of macroNFPA growth. On multivariable Cox regression, age and male sex remained significant [HR 1.01 (1.003-1.020) per year and 1.33 (1.05-1.69), respectively]. Hazard ratio

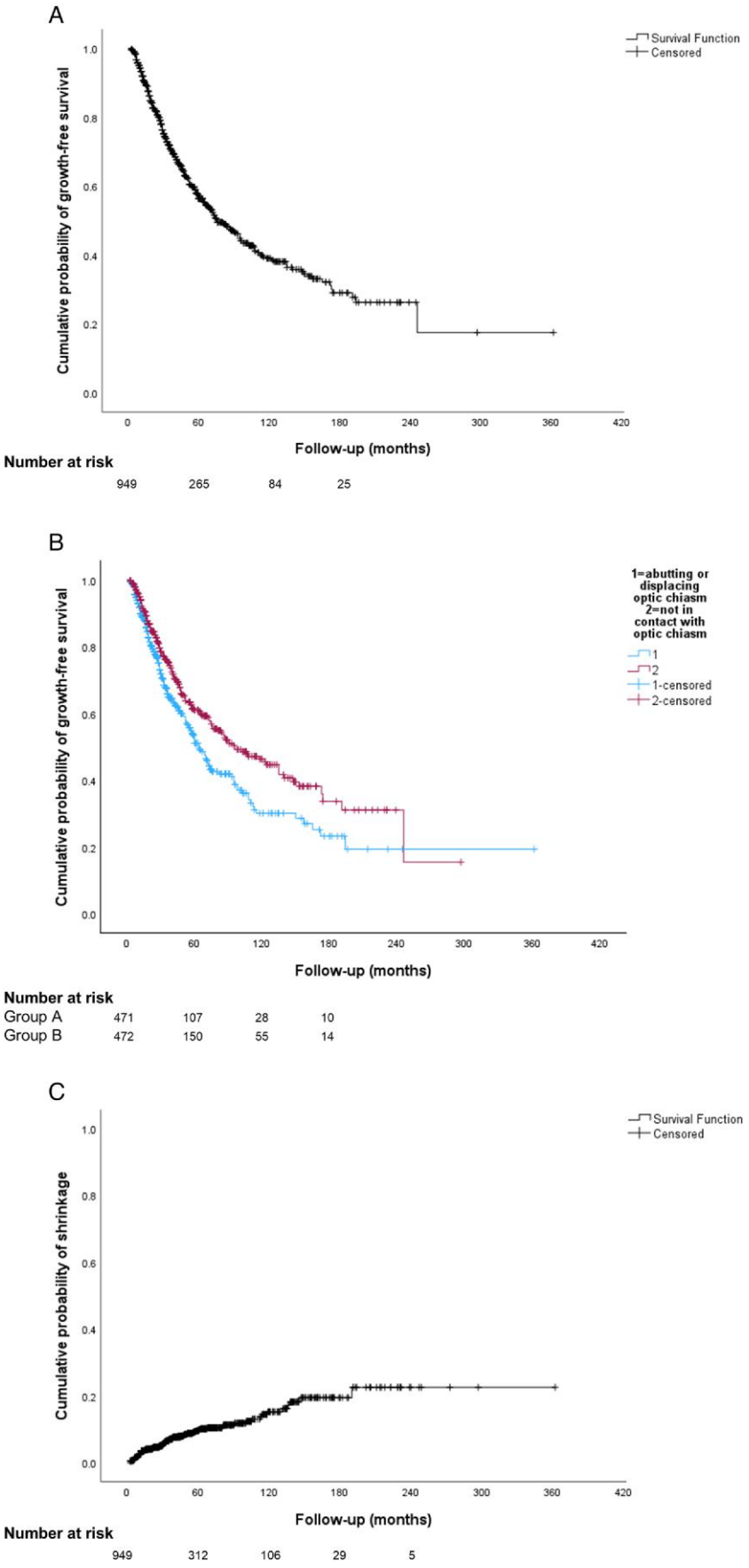

Figure 2. (A) Cumulative probability of non-functioning pituitary macroadenoma growth-free survival. (B) Cumulative probability of non-functioning pituitary macroadenoma growth-free survival for tumours abutting or displacing the optic chiasm (Group A), or not in contact with the optic chiasm (Group B) ($P = .002$). (C) Cumulative probability of non-functioning pituitary macroadenoma shrinkage.

Table 2. Cumulative probabilities of non-functioning pituitary macroadenoma growth-free survival or shrinkage.

Interval	Cumulative probability of tumour growth-free survival (95% CI) (first episode of enlargement)		
	Total group	Tumours abutting/displacing optic chiasm[a]	Tumours not in contact with optic chiasm[a]
6 months	98.4% (97.6-99.2)	98.1% (97.5-99.3)	98.7% (97.7-99.7)
1 year	91.9% (90.2-93.7)	89.9% (87.2-92.6)	94.0% (91.8-96.2)
2 years	81.6% (79.1-84.1)	78.5% (74.6-82.4)	84.5% (80.0-88.0)
3 years	70.8% (67.7-73.9)	65.9% (61.0-70.8)	75.6% (71.3-79.9)
5 years	56.4% (52.5-60.3)	51.1% (45.4-56.8)	61.1% (55.8-66.4)
Interval	**Cumulative probability of tumour growth-free survival (95% CI) (second episode of enlargement)**		
1 year	85.3% (80.0-90.6)		
2 years	66.2% (58.7-73.6)		
3 years	47.2% (40.0-55.4)		
Interval	**Cumulative probability of tumour shrinkage (95% CI) (first episode of shrinkage)**		
1 year	3.5% (2.3-4.7)		
3 years	7.1% (5.3-8.9)		
5 years	9.6% (7.2-12.0)		
Interval	**Cumulative probability of tumour shrinkage (95% CI) (second episode of shrinkage)**		
1 year	17.2% (7.0-27.4)		
3 years	42.4% (28.5-56.3)		

[a]$P = .002$ (log-rank test).
Abbreviations: CI, confidence interval.

for macroNFPAs with extensions compared with only intrasellar ones was 1.43 (0.996-2.060). Detailed HRs are given in Table 3.

After the first episode of macroNFPA enlargement, transsphenoidal surgery was offered to 135 patients and radiotherapy in 2 (reasons for conservative management were absence of visual dysfunction attributed to the macroNFPA 72.9%, poor surgical candidate 16.7%, patient's choice 8.3%, no deterioration of previous visual dysfunction 1.7%, and unknown 0.4%). From those conservatively managed, 177 had further imaging monitoring for a median period of 2.6 years (IQR 1.6-4.4). Further tumour growth was described in 103 (60.5%) [at a median interval of 2.2 years (IQR 1.1-3.5)] and shrinkage in 7 (4.0%) cases [at a median interval of 2.0 years (IQR 1.2-2.1)]. Cumulative probability of second growth was 14.7%, 33.8%, and 52.8% at 1-, 2-, and 3-year follow-up, respectively (Table 2).

Overall, during the whole observation period, 201 patients had transsphenoidal surgery. Reasons and pathology results are given in Table 4. The pituitary function outcomes of these patients are presented in Table 4.

Cumulative probability of tumour shrinkage was 3.5%, 7.1%, and 9.6% at 1-, 3-, and 5-year follow-up (Figure 2C and Table 2). Univariable Cox regression analysis showed that age at macroNFPA detection, sex, maximum diameter, cavernous sinus invasion, more than 1 extension, and tumour consistency on imaging at macroNFPA detection were predictors of tumour shrinkage. On multivariable Cox regression, sex and tumour consistency remained significant [HR for males 0.53 (0.32-0.87), HR for purely solid tumours compared with those with cystic component or haemorrhage 0.30 (0.19-0.48)]. Detailed HRs are given in Table 3.

From the 83 macroNFPAs that showed shrinkage, 53 had further follow-up (median 3.6 years, IQR 1.9-6.0). Amongst them, 4 demonstrated enlargement (22, 25, 54, and 82 months after identification of shrinkage); in 2 cases, there was no optic chiasm displacement or visual dysfunction and surveillance was opted, whereas in the other 2, transsphenoidal surgery was offered due to optic chiasm displacement or multiple growths (pathology confirmed null cell pituitary adenoma and gonadotroph adenoma, respectively). In the remaining patients, macroNFPA remained stable or continued to show reduction in size. Cumulative probability of further shrinkage on imaging was 17.2% and 42.4% at 1- and 3-year follow-up (Table 2).

Amongst the patients with intact pituitary hormone axes at the time of macroNFPA detection who had their pituitary function re-evaluated during follow-up, new FSH/LH deficiency was found in 25/541 (4.6%), new adrenocorticotropic hormone (ACTH) deficiency in 26/653 (4.0%), and new TSH deficiency in 31/636 (4.9%). During the period of radiological tumour stability, new FSH/LH, ACTH, and TSH deficiency developed in 9 (1.7%), 8 (1.2%), and 14 (2.2%) patients, respectively. When focusing only on the cases with growth of macroNFPA and re-evaluation of their pituitary function at that time, new FSH/LH deficiency was reported in 16/203 (7.9%), new ACTH deficiency in 18/255 (7.1%), and new TSH deficiency in 17/247 (6.9%).

Discussion

This is the largest study to date of patients with macroNFPA investigating outcomes when monitoring alone was the management approach at the time of tumour detection. During imaging follow-up of 4699 patient-years, the incidence rate of tumour enlargement was 9.8 per 100 patient-years. In a meta-analysis published in 2011 of 11 reports that enrolled ~260 patients with pituitary incidentaloma or presumed NFPA under monitoring, incidence rate for macroadenoma growth was 12.53 per 100 patient-years (95% CI, 7.86-17.20) with, however, significant heterogeneity across studies (I^2 99%).[19] In a more recent systematic review, this rate was not calculated in macroadenomas due to the high level of heterogeneity amongst published reports.[20]

Table 3. Hazard ratios for non-functioning pituitary macroadenoma enlargement and shrinkage during follow-up.

Variable	Univariable hazard ratio (95% CI)	Multivariable hazard ratio (95% CI)
	Tumour enlargement	
Age at macroNFPA detection	1.02 (1.01-1.02) per year, $P < 0.001$[a]	1.01 (1.003-1.020) per year, $P = .008$[a]
Patient sex (males vs females)	1.64 (1.32-2.02), $P < .001$	1.33 (1.05-1.69), $P = .018$
Maximum diameter at macroNFPA detection	1.03 (1.01-1.04) per mm, $P < .001$	1.003 (0.98-1.02) per mm, $P = 0.781$
MacroNFPA with cavernous sinus invasion	1.31 (1.05-1.65), $P = .019$	1.07 (0.71-1.62), $P = .738$
MacroNFPA with suprasellar extension vs only intrasellar or with other extensions	1.08 (0.88-1.32), $P = .482$	—
MacroNFPA with extensions vs only intrasellar	1.69 (1.24-2.29), $P < .001$	1.43 (0.996-2.060), $P = .052$
MacroNFPA with more than 1 extension	1.35 (1.07-1.70), $P = .011$	0.97 (0.64-1.48), $P = .884$
MacroNFPA abutting/displacing optic chiasm vs not in contact with optic chiasm	1.34 (1.13-1.69), $P = .002$	0.999 (0.78-1.28), $P = .991$
MacroNFPA purely solid vs with cystic component or haemorrhage on imaging	1.04 (0.79-1.37), $P = .781$	—
	Tumour shrinkage	
Age at macroNFPA detection	0.98 (0.97-0.99) per year, $P = .003$	0.998 (0.98-1.01) per year, $P = .793$
Patient sex (males vs females)	0.43 (0.27-0.67), $P < .001$	0.53 (0.32-0.87), $P = .012$
Maximum diameter at macroNFPA detection	0.94 (0.90-0.99) per mm, $P = .011$	0.97 (0.93-1.02), $P = .970$
MacroNFPA with cavernous sinus invasion	0.40 (0.20-0.80), $P = .010$	0.34 (0.12-1.18), $P = .095$
MacroNFPA with more than 1 extension	0.48 (0.25-0.93), $P = .030$	1.63 (0.56-4.75), $P = .370$
MacroNFPA purely solid vs with cystic component or haemorrhage on imaging	0.26 (0.17-0.42), $P < .001$	0.30 (0.19-0.48), $P < .001$

Patients who developed acute pituitary apoplexy during follow-up were not included in the analyses.
[a]Higher with advancing age.
Abbreviations: CI, confidence interval; macroNFPA, non-functioning pituitary macroadenoma.

In our study, the probability of macroNFPA growth at 6 months was 1.6%. Focusing on tumours not in contact with the optic chiasm at detection, this was 1.3% and, importantly, none of the tumours enlarging during the first 6 months led to visual field deterioration. Endocrine Society guidelines recommend pituitary MRI 6 months after the initial scan in all macroincidentalomas.[8] Our findings on tumours not in contact with the optic chiasm provide evidence for considering deferring the first follow-up scan to 1 year in this group.

The probability of growth increases with time; in our series, this reached 43.6% at 5 years. In a cohort with 24 non-operated macroNFPAs, growth rate was 43.8% at 4 years, and in a series of 35 incidentally found macroNFPAs, this was 51% at 5 years.[10,14] We found that a median time of tumour enlargement detection was 2.4 years. A series of 159 macroNFPAs with 3-year median follow-up reported median time to tumour growth of 4 years; in this study, however, patients presenting with mass effect (eg, visual fields defects) had been excluded, and the imaging protocol included annual MRI for the first 2 years extending to 2 yearly if tumour remained stable.[21]

Tumours abutting or displacing optic chiasm had a higher probability of enlargement (34.1% and 48.9% at 3 and 5 years, respectively), compared with those not in contact with it. In patients in this group not managed by surgery, imaging and visual assessment at 6 months, followed by annual scans and regular visual review (every 6-12 months), is required, but also considering the patient's comorbidities, frailty, and suitability for surgical intervention. A study of 42 presumed NFPAs (37 macroadenomas) with a mean follow-up of 61.9 months reported a higher probability of symptomatic enlargement in tumours with height exceeding 15 mm on detection compared with those <15 mm.[16]

It is of note that amongst our 301 cases with tumours abutting optic chiasm and not causing visual field defects, deterioration of visual fields was subsequently detected in 43 patients, with visual improvement achieved in most of those offered surgery (22 out of 24 with available data). In this group, cautious monitoring of vision with prompt surgical intervention, if visual function becomes affected by the tumour, could be considered as a management approach. In agreement with these data, in a study of 81 cases of NFPA with documented optic nerve compression on MRI but no deterioration of visual fields and mean follow-up 65.7 months, 14 patients experienced visual deterioration; 12 had surgery and vision normalized or improved in all.[22]

In tumours not in contact with the optic chiasm, growth rates were 24.4% and 38.9% at 3 and 5 years, respectively. Although around half of the enlarging tumours in this group were abutting or displacing the optic chiasm, deterioration of visual fields was reported in only 7%, a morbidity that improved or reversed completely in almost all patients post-surgery. This optimal visual outcome relates to the early detection and intervention. The intensity of imaging surveillance in this group would mainly depend on the distance from the optic chiasm; it has been proposed that for adenomas ≥5 mm far from optic chiasm, MRI could be performed in 1 year and in cases of stability, imaging could be arranged at 2-yearly intervals with a gradual reduction of frequency thereafter.[9] In cases closer to optic chiasm but not abutting it, yearly MRIs would be a reasonable approach (mainly aiming for early detection of visual compromise), with the decision on gradual frequency reduction being individualized. In an attempt to inform follow-up protocols, previous studies have proposed various cut-offs of tumour volume growth rates as predictors of enlargement or of worsening visual function or of surgery.[21,23] It should be noted, however, that methodological issues challenge the value of these estimates (eg, assumption that growth rate is constant over time, evaluation of tumour volume growth rates from measurements between the first and second MRI studies only, challenges on the reliable calculation of volume in tumours like pituitary adenomas). It is also interesting to note that in a report of 35 incidentally found macroNFPAs with 50-month median radiological monitoring, a wide range

Table 4. Reasons for transsphenoidal surgery, pathology results, and pituitary function outcomes after transsphenoidal surgery.

Reason for pituitary surgery	Number of patients
MacroNFPA enlargement	171
Visual deterioration without documented macroNFPA growth on imaging	13
Development of pituitary apoplexy	5
Patient's and/or clinician's decision without tumour enlargement or visual impairment	12

Pathology results[a]	Number of patients
Gonadotroph adenoma	100
Adenoma with negative staining for pituitary hormones	53
Corticotroph adenoma	14
Pluri-hormonal adenoma	4
Adenoma of Pit-1 lineage	3
Necrotic/haemorrhagic adenoma with no viable tissue available for immunohistochemistry	4
No evidence of tumour in the pathology specimen	2
Adenoma with no immunohistochemistry available	1

Outcome	Gonadotroph axis	ACTH axis	TSH axis	Permanent diabetes insipidus (vasopressin deficiency)
Reversal of pre-operative pituitary hormone deficit[b]	16/94 (17.0%)	9/56 (16.1%)	8/69 (11.6%)	—
New post-operative pituitary hormone deficit[c]	12/80 (15.0%)	17/117 (14.5%)	13/108 (12.0%)	6/172 (3.5%)

[a]Data available for 181 cases. [b]Denominator is the number of patients with pituitary hormone deficit pre-operatively. [c]Denominator is the number of patients with intact pituitary hormone axis pre-operatively. Patients who had surgery for pituitary apoplexy have been excluded.
Abbreviations: MacroNFPA, non-functioning pituitary macroadenoma; Pit-1, pituitary-specific positive transcription factor 1; ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone.

in the median increase in tumour size was found (0.3-3.9 mm/year).[10]

The duration of imaging surveillance is unclear, as studies with very long follow-up are lacking. Nonetheless, considering that macroNFPAs remain at risk of regrowth even 10 years after surgical removal,[24,25] progression of a macroNFPAs under observation in the long-term cannot be excluded, and discharge, especially of younger patients, would not be advisable.

On multivariable analysis, only advancing age and male gender were associated with a higher risk of macroNFPA enlargement. There was also a trend for growth in macroNFPAs with extension outside the sella, as opposed to those only confined to the sella. A previous small study (29 macroNFPAs) did not find an association of growth with clinical or imaging parameters, but the small sample size is the likely reason for lack of positive findings.[15]

To our knowledge, this is the first study reviewing outcomes of patients not offered surgery after the first episode of macroNFPA enlargement. During 2.6-year median observation period, further growth occurred in 60.5% of cases (cumulative probability 33.8% at 2 years), stability in 35.5%, and shrinkage in 4.0%. These results confirm the variable behaviour and non-constant growth pattern of these tumours, and within the constraints of short follow-up, they provide evidence that non-clinically significant growth is not necessarily an absolute indication for surgery, as, in several cases, progression may not continue.

We found that after transsphenoidal surgery performed by various surgeons, reversal of hypopituitarism was unlikely (12%-17% for each axis) and that the rate of additional anterior pituitary hormone deficits ranged between 12% and 15%, with permanent diabetes insipidus (vasopressin deficiency) at 3.5%. Endocrine Society guidelines suggest (but not recommend) that surgery is considered for patients with pituitary incidentaloma if there is loss of endocrinological function.[8] Our results, however, would not support this approach.

Tumour shrinkage was observed in a small number of cases with 9.6% 5-year probability. Presence of cystic or haemorrhagic components on imaging was a factor associated with this outcome. Probability of further shrinkage was 42.4% at 3 years, but the identification of cases with subsequent stability or, rarely, enlargement confirms, again, the variable behaviour of macroNFPAs.

During follow-up, detection of new pituitary hormone deficits was found at low rate (4.0%-4.9% for each axis) and was mainly observed in cases with tumour enlargement. Focusing only on patients with tumour growth, there rates remained relatively low (6.9%-7.9% of each axis). In a recent systematic review, incidence of new endocrinopathies in conservatively managed macroadenomas was reported 1.5 per 100 patient-years, but details on type of deficits and whether these were attributed to tumour growth were not provided.[20] Endocrine Society guidelines recommend biochemical assessment for hypopituitarism 6 months after initial testing and yearly thereafter in pituitary macroincidentalomas.[8] A similar protocol is proposed by the French Endocrinology Society.[9] Our data challenge these recommendations, and the clinical value and cost-effectiveness of regular pituitary function assessment in cases with stable tumour need to be reviewed.

Strengths of our study include the large number of patients (to the best of our knowledge, the largest cohort published to date) allowing estimates with high confidence, and its multicentre design, which facilitated wide representation of the practice of UK endocrine departments and inclusion of diverse groups of patients (UK NFPA consortium). By focusing on all and not specific groups of presumed macroNFPAs managed conservatively, we avoided selection bias, and this approach allowed us to draw conclusions on the natural history of these tumours in a holistic way. Importantly, we provided outcomes of subsequent surgical interventions and data on tumour behaviour after the first episode of growth or shrinkage. Limitations include lack of pathological verification of

adenoma diagnosis, which was unavoidable, as our aim was to investigate outcomes of conservatively managed cases. Nonetheless, the positive pathology reports of those operated provide reassurance. Variation in the interpretation of scans between radiologists from the collaborating centres needs to be taken into consideration and relates to the retrospective nature of this multicentre study. It should be noted, however, that our results reflect "real-world' clinical practice in our centres. Studies of similar magnitude from other countries would enhance the generalizability of our results. Death was not considered as competing risk in the Kaplan–Meier analyses. Finally, a median monitoring duration was 3.6 years but this, to some extent, was related to the fact that 21% of patients eventually had surgery.

Our multicentre study has addressed areas of uncertainty in the natural history and outcomes of conservatively managed macroNFPAs. Our data can inform clinical practice, the intensity of imaging surveillance, and set the groundwork for revising published guidelines. We have shown that, in contrast to non-functioning pituitary microadenomas,[26] macroNFPAs have high probability of growth over time. However, in tumours not in contact with the optic chiasm, this is lower, and our results suggest that follow-up imaging as early as 6 months is not necessary. New visual field defects are mostly reversible if diagnosed and managed promptly, and therefore, for lesions abutting optic chiasm with normal visual fields, ophthalmologic and imaging monitoring should be individualized with the patient. Once enlargement is identified, further growth is highly likely; nonetheless, stability or shrinkage may also occur. Development of new hypopituitarism in radiographically stable tumours is very rare, challenging the necessity of regular pituitary function assessment; nonetheless, this should be organized if there is clinical suspicion of hypopituitarism. Studies with longer follow-up will contribute to further elucidation of the behaviour of these tumours.

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Authors' contributions

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