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Natural History of Non-Functioning Pituitary Adenomas: A Systematic Review and Meta-Analysis

Authors
Stefan Dukanovic Rikvold[1], Mathias Brown Pedersen[1], Mikkel Andreassen[1], Jesper Krogh[2]

Affiliations
1 Department of Endocrinology and Metabolism, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark
2 Department of Medicine, Clinic for Pituitary Disorders, Zealand University Hospital – Koge, Denmark

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Georg Thieme Verlag, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence
Dr. Jesper Krogh
Zealand University Hospital Koge,
Department of Endocrinology,
Lykkebækvej 1
4600 Koge
Denmark
Tel.: +45 25535485, Fax: +45 25535485
jesper.krogh@dadlnet.dk

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ABSTRACT

The management of non-functioning pituitary tumors (NFPTs) relies on the risk of tumor growth and new endocrinopathies. The objective of this systematic review was to assess the risk of growth, new pituitary endocrinopathies, and surgery in patients with conservatively treated NFPTs. We conducted a bibliographical search identifying studies assessing NFPTs followed conservatively. Estimates were pooled using random-effects meta-analysis reporting events per 100 person years (PYs), in case of high heterogeneity (I2 > 75 %) only the range of observed effects was reported. We identified 30 cohort studies including 1957 patients with a mean follow-up time of 4.0 (SD 1.5) years. The overall risk of tumor growth ranged from 0.0 to 14.2/100 PYs (I2 = 90 %), while the overall risk of new endocrinopathies was 0.9/100 PYs (95 % CI. 0.5 to 1.2; I2 = 35 %) and risk of surgery ranged from 0.0 to 7.7/100 PYs (I2 = 80 %). Compared to microadenomas, macroadenomas had higher risk of growth (p = 0.002), higher risk of surgery (p = 0.006), and non-significant differences in risk of new endocrinopathies (p = 0.15). An analysis of microadenomas found the risk of growth to be 1.8/100 PYs (95 % CI. 0.9 to 2.8; I2 = 58 %), the risk of new endocrinopathies 0.7/100 PYs (95 % CI. 0.0 to 1.6; I2 = 37 %) and the risk of surgery 0.5/100 PYs (0.1 to 0.9; I2 = 37 %). These data support individualized follow-up strategies of patients with NFPTs and particularly a less rigorous follow-up of patients with microadenomas.

Introduction

Non-functioning pituitary tumors (NFPTs) are non-secreting benign tumors of the pituitary gland and are diagnosed due to endocrinopathies or mass effect causing visual defects, or as nonfunctioning pituitary incidentalomas (NFPIs) on imaging performed for purposes not related to the pituitary gland [1]. Transsphenoidal surgery, or a combination of surgery and radiotherapy, is recommended as the primary treatment for NFPTs causing mass effect symptoms [2] while surgery of hypopituitarism is considered a relative indication [3]. However, conservative management of NFPTs in respect to frequency of imaging and biochemical assessment of pituitary function relies on risk estimates of tumor growth and development of new endocrinopathies, that is, natural history of NFPTs.

A previous review regarding the natural history of NFPTs reported risk of growth of 12.5/100 person years (PYs) for macroadenomas and 3.3/100 PYs for microadenomas [1]. However, both estimates were associated with substantial heterogeneity and therefore do not represent reliable estimates. Two recent cohort studies of 197 patients with NFPTs and 203 patients with NFPIs observed tumor growth in 44 % of patients with NFPTs and in 15 % of patients with NFPIs during a follow-up period of 3 years [4, 5]. Apart from tumor size, solid lesions have been associated with higher risk of tumor growth compared to cystic lesions. A previous systematic

review reported an estimate of 2.4/100 PYs for developing new endocrinopathies during follow-up [1]. Two larger studies [4, 5] reported that 20 to 24 % of patients had hormone deficiencies at baseline, being more prevalent in macroadenomas, in older individuals, and in males. In these studies, 5 % experienced new endocrine dysfunction during a 3-year follow-up. In 2017, WHO re-classified pituitary tumors based on hormonal as well as transcription factor immunohistochemistry and also classified certain tumor types as having a high risk of recurrence [6]. Assessments of surgically treated patients with pituitary tumors found that 50 % of tumors classified as high-risk tumors were prior to surgery classified as non-functioning illustrating the growth potential in sub-types of NFPTs [7, 8] It is stressed in multiple studies [1, 5, 9] that the evidence regarding the natural history of NFPTs/NFPIs is scarce and of low quality due to heterogeneity/inconsistency, methodological limitations, and imprecision caused by small number of events. Since the systematic review from 2011 by Fernandez-Balsells et al. [1] a more recent review from 2022 by Pernik et al. has been published [10], which did not include recent important studies [11, 12]. Both reviews report pooled estimates associated with large heterogeneity [1, 10] and one report estimates on risk of growth irrespective of follow-up time [10]. While previous review report on the risk of growth of pituitary tumors, they have failed to report on the more clinically relevant outcome of surgical intervention. Therefore, an updated review is called for, in order to guide management of patients with NFPTs with respect to frequency of pituitary scan and frequency of testing for pituitary endocrinopathies.

Objective

The objective of this systematic review was to assess the incidence of tumor growth, new pituitary endocrinopathies, and the need for active treatment, that is, surgery and/or radiotherapy, in conservatively treated NFPTs.

Materials and Methods

Design

A systematic review of observational studies. The protocol has been registered at PROSPERO (CRD42020219825).

Eligibility and inclusion criteria

Eligible studies were observational studies that followed patients with NFPTs found on CT- and/or MRI-scan and without the need for initial surgery or radiotherapy within 3 months from baseline. Studies enrolling less than 5 patients were excluded. There were no language restrictions or restrictions on publication date.

Outcomes

The primary outcomes were the proportion of patients with increase in tumor size, new endocrinopathies, and the need for active treatment, that is, surgery or radiotherapy, reported as yearly incidence per 100 person years (PYs). Secondary outcomes were new visual defects and pituitary apoplexy. Exploratory outcomes were the failure or recovery of specific pituitary hormonal axes and proportion of patients with tumor shrinkage.

Identification of studies

A search of PubMed and EMBASE from inception to present date was conducted using text words and MeSH terms as shown in **Table S1**. Reference lists of included studies and relevant reviews were searched for additional eligible studies.

Selection of studies

One investigator conducted the selection process (SD). After eliminating duplicate studies, the remaining studies were evaluated based on title and abstract, and potentially eligible studies were selected for full text reading.

Data extraction

Using a standardized predefined procedure, outcomes from each study were collected as well as the following study characteristics: country of origin, study design, study intervention, study period, and duration of follow-up as well as baseline patient characteristics: number of patients, gender, age, macro- vs. microadenomas, baseline tumor size, baseline endocrine pituitary function as failure of any axis as well as failure of a specific pituitary hormonal axis, and baseline visual status.

Assessment of study quality

We expected to include cohort studies that did not include comparator groups and classical bias assessment was therefore not appropriate. However, some study characteristics may still be responsible for over- or underestimation of outcomes and each study was characterized on six domains: Study design, reporting of confounders, consecutive enrollment, outcome assessment, missing data and selective outcome reporting.

Study design was described as prospective or retrospective and confounders for tumor growth included tumor size at baseline as well as describing inclusion of cystic tumors, while confounders for new endocrinopathies were baseline assessment of anterior lobe hormones apart from prolactin. Patients were considered consecutively enrolled if all patients within a defined time period, fulfilling all inclusion criteria and none of exclusion criteria, were enrolled in the study. Outcome assessment was considered structured in case scanning or hormone assessment intervals were predefined the first three years from baseline, allowing for extra scan or hormonal assessment in case of clinical necessity. A study was classified as having missing data in case more than ten percent of included participants were not included in the study results while selective outcome reporting was classified in case tumor growth was not reported or only reported if the tumor grew more than a pre-specified number of millimeters.

Statistics

All outcomes were expressed as proportions and incidence rates per 100 person years (PYs) with an associated 95 % confidence interval (CI). The reported number of study participants and mean duration of follow-up was used for the calculation of total follow-up time. We expected that study populations may differ, and a random effects model was chosen for calculation of weighted estimates, that is, meta-analysis. Heterogeneity was assessed using the I^2-statistic, which yielded the proportion of differences in effect size, which was caused by true differences in effect, rather than sto-

chastical variation. Low, moderate, and high levels of inconsistency were defined as I^2 values of 25 %, 50 %, and 75 %, respectively, and in case the I^2 > 75 % we abstained from conducting a meta-analysis and only reported the range of reported study effects. Study or patient characteristics reported in medians were converted to means using a standard formula [13]. All analyses are presented including all relevant studies, in case a study was considered an outlier by visual inspection, a supplementary analysis was conducted excluding the outlier. Publication bias was assessed by visual inspection of forest plots for the primary outcomes and in case these were considered skewed, Egger's test was performed in order to qualify this observation and secondly a Duval and Tweedie's trim and fill procedure were conducted to estimate potential impact of publication bias. Meta-analysis was conducted using Comprehensive Meta-analysis 3.1, and p-values ≤ 0.05 were considered significant.

Subgroup-analyses

Causes of heterogeneity were explored by comparing studies with low and high proportions of macroadenomas, male subjects, and high age as well as comparing studies with short and long follow-up time. The splitting of studies into two groups was based on median values of each study characteristic. Variables were also assessed for impact on outcome using meta-regression. To assess the differences in estimates for micro- and macroadenomas we conducted direct comparison of events in studies including both micro- and macroadenomas, which would provide number of events obtained in the same settings and conditions rather than compare studies limited to only one tumor size.

Deviations from the protocol

Baseline tumor extension, baseline Knosp grade, baseline co-morbidities, and time from diagnosis to active treatment were not collected due to lack of systematic reporting.

Results

The last search was conducted the 7th of May 2023 and as shown in ▶ **Fig. 1**, ▶ **Table 1**, and **Table S2**, we included 35 publications reporting on 30 studies [4, 5, 11, 12, 14–39]. The included studies represent data from 1957 patients with NFPTs who were initially treated conservatively and followed for a mean of 4.0 (SD 1.5) years. Two of the included studies followed a total of 69 patients with Multiple Endocrine Neoplasia, type 1 (MEN1) [28, 37] and two studies followed 99 children [12, 39]. The mean of study participants mean age was 48.2 years (SD 15), while the mean proportion of male subjects was 46 (SD 15) percent. At baseline, the mean proportion of macroadenomas in each study was 55 (SD 36) percent, the mean proportion of participants with any pituitary deficiency was 26 (SD 25) percent, and 12 (SD 18) percent had visual deficiencies.

Quality of studies

As shown in Table S4, 1 of 30 studies was classified as a prospective study, information on tumor size at baseline as well as proportion of cystic tumors were reported in 6 of 30 studies, while baseline endocrinopathies were reported in 17 of 30 studies. Missing data, regarding tumor size and development of new endocrinopathies, was observed in 11 and 15 of 30 studies.

Primary outcomes

Tumor growth

During follow-up, tumor growth was observed in 422/1914 (22.0 %) patients, however, assessed as events per 100 PYs the between study heterogeneity was high (I^2 = 89 %) ranging from a risk of 0.5 to 14.2/100 PYs as shown in ▶ **Table 2** and ▶ **Table 3**. Exploring causes of heterogeneity, we found that studies with a high proportion of macroadenomas reported a higher risk of tumor growth while mean age, proportion of males, and mean follow-up time did not explain heterogeneity (**Table S5**) and further exploration of heterogeneity using meta-regression confirmed these findings while suggesting that increasing age may be associated with tumor growth: proportion of macro-adenomas (p = 0.006), mean age (p = 0.03), proportion of males (p = 0.13), and the mean follow-up time (p = 0.72).

As shown in ▶ **Table 3**, high heterogeneity (82 %) was still present limiting the analysis to macroadenomas, while the pooled estimate of growth in microadenomas was 1.8/100 PYs (95 % CI; 0.9 to 2.8; I^2 = 58 %). Excluding one outlier [30] reporting a very high risk of growth in microadenomas, the risk of growth was reduced to 1.6/100 PYs (95 % CI; 0.8 to 2.4; I^2 = 49 %). Analysis comparing the risk of growth in studies including both micro- and macroadenomas showed significant lower risk of growth in macroadenomas compared to microadenomas (p = 0.002), as shown in **Table S5**.

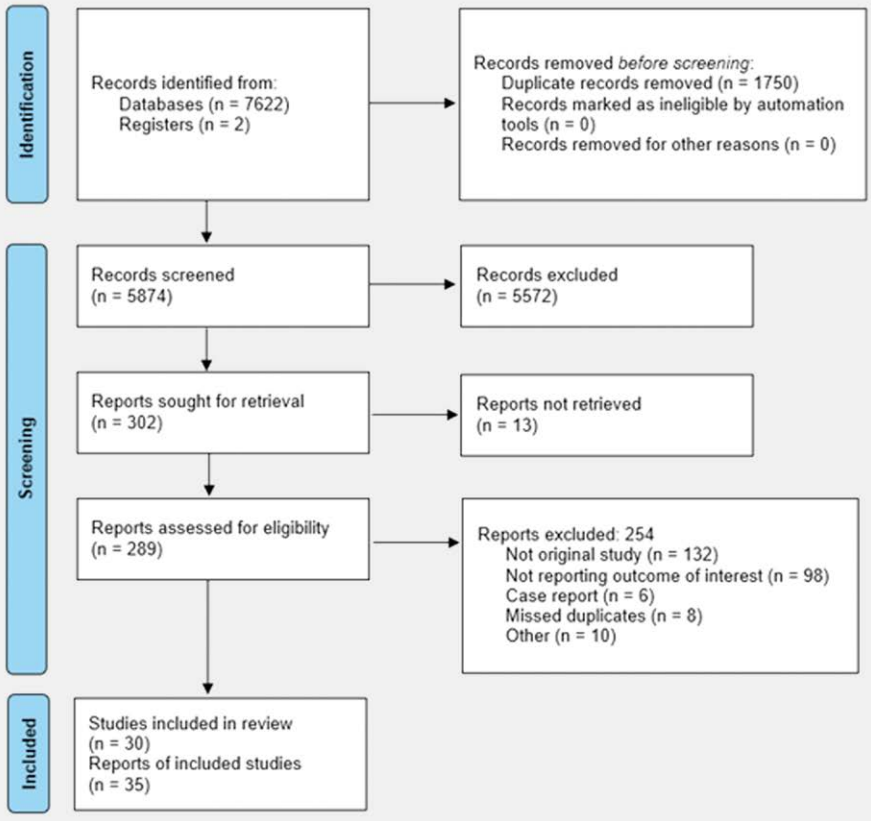
New endocrinopathies

A total of 40/1007 (4.0 %) patients developed a new pituitary endocrinopathy during follow-up, corresponding to a risk estimate of 0.9/100 PYs (95 % CI; 0.5 to 1.2; I^2 = 35 %). Subgroup analysis found that studies with > 39 % males had a higher risk of developing new endocrinopathies during follow-up, which was not confirmed using meta-regression analysis. As shown in **Table S6**, analysis of the other pre-planned subgroups did not explain the observed heterogeneity. There were no significant associations between the explored subgroups and risk of events assessed by meta-regression: mean age (p = 0.66), proportion of males (p = 0.19), proportion of macroadenomas (p = 0.08), or mean follow-up (p = 0.76).

In macroadenomas, the risk of developing new endocrinopathies was 1.5 (95 % CI; 0.9 to 2.1; I^2 = 0 %) compared to 0.7 (95 % CI; 0.0 to 1.6; I^2 = 37 %). Limiting the analysis to studies including both micro- and macroadenomas the risk of new endocrinopathies was 0.9/100 PYs in microadenomas compared to 2.1/100 PYs, which was not significantly different (p = 0.15).

Active treatment

During follow-up the total number of patients with the need for active treatment was 119/1603 (7.4 %), ranging from 0 to 7.7/100 PYs with large heterogeneity, I^2 = 80 %. Among all patients receiving active treatment only one patient received RT [18], while the rest underwent pituitary surgery. As shown in **Table S7**, none of subgroup analyses explained any of the observed heterogeneity. Exploring the influence of subgroups using meta-regression supported the above findings: mean age (p = 0.02), proportion of males



▶ **Fig. 1** Identification and selection of included studies.

(p = 0.95), proportion of macroadenomas (p = 0.05), and mean follow-up (p = 0.78). A separate analysis of macroadenomas found the risk of surgery to be 3.1/100 PYs (2.1 to 4.1; I^2 = 52 %) compared to 0.5 PYs (95 % CI; 2.1 to 4.1; I^2 = 37 %) in microadenomas. This was confirmed in a formal analysis assessing studies including both micro- as well as macroadenomas finding the risk of active treatment significantly higher in macroadenomas (p = 0.001).

Publication bias

Inspection of the funnel plots suggested that studies reporting low incidence risk was missing for all primary outcomes, a finding which was supported by Egger's test (all p < 0.04). Using Duval and Tweedie's trim and fill procedure the overall estimate was reduced by 0.1, 0.3, and 0.5/100 PYs for growth, new endocrinopathies, and active treatment. Year of publication did not affect any of the primary outcomes in meta-regression analysis (all p-values > 0.25).

Secondary outcomes

During follow-up the total number of patients with new visual deficiencies was 70/992 (7.1 %), with the lowest and highest reported incidence being 0.0 to 9.8/100 PYs with an associated I^2 of 78 % and as shown in ▶ **Table 3**, a new visual defect only occurred in 1 of 403 patients with microadenomas. Pituitary apoplexies occurred in 21/826 (2.5 %) patients corresponding to an incidence of 0.4 100/PYs with an associated I^2 of 23 %.

Exploratory outcomes

Tumor shrinkage was observed with an incidence between 1.3 to 19.7/100 PYs (I^2 = 80 %), however, removing one outlier [24] the incidence of tumor shrinkage across studies was estimated to 3.7/100 PYs as shown in ▶ **Table 3**, while the overall risk of recovery of any pituitary function was estimated to 1.2/100 PYs.

Failure of a specific hormonal axis was only reported in four studies (**Table S3**) with risk of ACTH-failure having the highest risk of 0.8/100 PYs as shown in **Table S8**. No studies reported on the risk of diabetes insipidus.

Discussion

This systematic review, including 1957 conservatively treated NFPTs followed for a mean of 4.0 years, found that the reported risk of tumor growth and surgical interventions was higher in macroadenomas compared to microadenomas. While this difference was also observed in the risk of new endocrinopathies it did not reach statistical significance. The important patient outcomes of surgery, new endocrinopathies, or deterioration of visual function was all below 1.0/100 PYs in patients with microadenomas.

Strengths and limitations

A major strength of this systematic review is the rigorous bibliographical search strategy, a published protocol, bias assessment of

▶ **Table 1** Baseline characteristics of studies assessing progression of conservatively treated non-functioning pituitary tumors.

Author [Ref], Year of publ.	n (mean age)	Male (%)	MacroA (%)	Endocrinop. (E) Visu. Defect (V)	Scan	Years of follow-up, mean (range)
Reincke [14], 1990	14 NFPI (41)	3/14 (21)	7/14 (50)	E: 3/14 V: 0/14	Yearly	3.2 (0.9 to 8)
Donovan [15], 1995	31 NFPI (35)	11/31 (35)	16/31 (52)	E: 0/31 V: 0/31	After 6 mo. – then yearly	6.4 (3 to 11)
Nishizawa [16], 1998	28 NFPI (63)	13/28 (46)	28/28 (100)	E: 7/28 V: 0/31	Yearly	5.6 (0.5 to 10)
Feldkamp [17], 1999	50 NFPI (NR)	NR	19/50 (38)	E: NR V: 0/50	After 3 mo. – then yearly	2.7
Igarashi [18], 1999	23 NFPT (47)	10/23 (44)	22/23 (96)	E: 1/23 V: 8/23	NR	5.1 (1.5 to 11.6)
Oyama [19], 2005	289 NFPI (49)	130/289 (45)	NR	E: NR V: 0/289	After 3 mo. – then NR	2.3 (0.5 to 14.5)
Vilar [20], 2005	12 NFPI (NR)	NR	4/12 (33)	E: NR V: NR	NR	2.8
Arita [21], 2006	42 NFPI (61)	18/42 (43)	37/42 (88)	E: NR V: 0/42	After 6 mo. – then yearly	5.2 (0.9 to 14.0)
Dekkers [22], 2007	28 NFPT (55)	15/28 (54)	28/28 (100)	E: 20/28 V: 13/28	Yearly or every 2 year	7.1
Karavitaki [23], 2007	40 NFPT (52)	18/40 (45)	24/40 (60)	E: 11/40 V: 5/40	Every 1–2 years	3.5 (0.7 to 10.7)
Carsote [24], 2009	69 NFPT (NR)	NR	0/69 (0)	E: 0/69 V: NR	NR	2.5 (0.8 to 8)
Cury [25], 2009	13 NFPT (NR)	NR	NR	E: 9/13 V: 7/13	NR	6.9
Ryu [26], 2010	6 NFPT (66)	5/6 (83)	6/6 (100)	E: NR V: 1/6	Every 6–12 mo.	3.4
Anagnostis [27], 2011	23 NFPT (NR)	NR	6/23 (26)	E: NR V: NR	At least yearly	4.6
de Laat [28], 2015	45 NFPT (NR)	NR	6/45 (13)	E: NR V: NR	NC	5.5
Karamouzis [29], 2015	33 NFPT (60)	21/33 (64)	27/33 (82)	E: NR V: NR	At least yearly	4.5 (1 to12)
Sam [30], 2015	66 NFPT (41)	28/66 (42)	47/66 (71)	E: 40/66 V: 5/66	Every 6–12 mo.	4.3 (1 to14.7)
Vargas [31], 2015	19 NFPT (NR)	NR	NR	E: NR V: NR	NR	NR
Imran [32], 2016	99 NFPI (NC)	NR	NR	E: NR V: NR	Every 6–12 mo.	3.0
Lenders [33], 2016	50 NFPT (49)	15/50 (30)	23/50 (46)	E: 4/50 V: 0/50	NR	3.0 (0.5 to 6.6)
Iglesias [34], 2017	26 NFPI (NR)	NR	9/26 (35)	NR	Yearly or more	1.3
Kim [4], 2018	197 NFPT (53)	96/197 (49)	159/197 (81)	E: 40/197 V: 0/197	Yearly for 2 years	3.1
Levy [35], 2018	65 NFPT (68)	37/65 (57)	65/65 (100)	E: NR V: 23/65	After 6 mo. then clinics	5.0
Stalldecker [36], 2019	11 NFPT (>65)	NR	NR	E: NR V: 1/11	NR	3.6
Thaker [12], 2019	44 NFPT (14)	8/44 (18)	3/44 (6.8)	E: 7/44 V: 0/44	Yearly	4.5
Wu [37], 2019	24 NFPT (44)	12/24 (50)	NR	E: NR V: NR	NR	2.9 (0.5 to 7.3)
Hwang [38], 2020	81 NFPT (58)	48/81 (59)	81/81 (100)	E: 0/81 V: 0/81	Every 2 year	5.5
Tresoldi [5], 2020	203 NFPI (50)	NR	71/203 (35)	E: NR V: 63/177	After 6–12 mo.	3
Han [11], 2022	271 NFPT (NR)	NR	0/271 (0)	E: NR V: 0/271	NR	2.4 (0 to 12.8)
Borghammar [39], 2023	55 NFPT (12)	24/55 (44)	0/55 (0)	E: 22/55 V: 0/55	NR	3 (0.3 to 15.8)

NR: Not reported or unclear; MacroA: Macroadenoma; mo.: Months; NFPT: Non-functioning pituitary tumors; NFPI: Non-functioning pituitary incidentalomas.

included studies, pre-defined subgroup analysis, and a transparent reporting. Also, separate analysis of micro- and macroadenomas across several outcomes provides strong and clinical meaningful estimates for these separate entities. However, funnel plot of primary outcomes suggested that studies with lower incidence rates was missing and that the pooled estimates may be lower. In case the funnel plots represent true bias, the trim and fill procedure did not change the estimated incidences in a magnitude that changed the interpretation of current results. The calculation of observed patients' years was based on mean follow-up times opposed to individual follow-up time, which may distort the estimates in either direction. Frequency of scans, definition of growth, testing of pituitary function and indications for pituitary surgery may differ from study to study, which all may contribute to heterogeneity of the observed results.

Primary outcomes

The risk of tumor growth overall and for macroadenomas was associated with high heterogeneity with a range of reported incidence for growth of macroadenomas between 0 and 19.5/100 PYs. A previous review found a risk of growth of macroadenomas of 12.5/100 PYs, an estimate associated with an $I^2 = 99\,\%$ [1]. In the current study, only 5 of 20 studies report incidence rates beyond 12.5 and it likely that the true incidence rates are lower. In a subgroup analysis of studies including both micro- and macroadenomas the estimate for growth in macroadenomas was 7.0/100 PYs,

▶ **Table 2** Events during follow-up of conservatively treated non-functioning pituitary tumors.

Study [ref], Year of publ.	Growth All tumors	Growth MacroA	Surgery All tumors	Surgery MacroA	New endocrinop. All tumors	New endocrinop. MacroA	Visual deterioration All tumors
	Events/total						
Reincke [14], 1990	3/14	2/7	0/14	0/7	1/14	1/7	0/14
Donovan [15], 1995	4/31	4/16	1/31	1/16	0/31	0/16	1/31
Nishizawa [16], 1998	1/28	1/28	2/28	2/28	NR	NR	2/28
Feldkamp [17], 1999	6/50	5/19	NR	NR	NR	NR	0/50
Igarashi [18], 1999	9/23	9/22	9/23	9/22	NR	NR	9/23
Oyama [19], 2005	30/289	NR	11/289	NR	NR	NR	NR
Vilar [20], 2005	1/12	1/4	2/12	1/4	NR	NR	NR
Arita [21], 2006	21/42	19/37	12/42	9/37	NR	NR	NR
Dekkers [22], 2007	14/28	14/28	6/28	6/28	3/28	3/28	9/28
Karavitaki [23], 2007	14/40	12/24	8/40	8/24	NR	NR	8/40
Carsote [24], 2009	19/69	0/0	NR	NR	NR	NR	NR
Cury [25], 2009	0/13	NR	0/13	0/13	0/13	NR	0/13
Ryu [26], 2010	4/6	4/6	1/6	1/6	NR	NR	2/6
Anagnostis [27], 2011	1/23	1/6	NR	NR	NR	NR	NR
de Laat [28], 2015	3/45	0/6	1/45	1/6	0/45	0/6	NR
Karamouzis [29], 2015	5/33	4/27	NR	NR	NR	NR	NR
Sam [30], 2015	38/66	28/47	9/66	9/47	NR	NR	9/66
Vargas [31], 2015	6/19	NR	NR	NR	NR	NR	NR
Imran [32], 2016	20/99	NR	NR	NR	1/77	NR	NR
Lenders [33], 2016	11/50	9/23	6/50	5/23	2/50	2/23	1/50
Iglesias [34], 2016	1/26	0/9	NR	NR	NR	NR	NR
Kim [4], 2018	87/197	NR	8/197	8/159	8/197	8/159	5/197
Levy [35], 2018	23/65	23/65	13/65	13/65	NR	NR	NR
Stalldecker [36], 2019	1/11	NR	NR	NR	0/11	NR	1/11
Thaker [12], 2019	1/44	0/3	0/44	0/3	NR	NR	0/44
Wu [37], 2019	NR	NR	NR	NR	NR	NR	NR
Hwang [38], 2020	51/81	51/81	16/81	16/81	10/81	10/81	14/81
Tresoldi [5], 2020	31/203	19/71	13/203	12/71	10/194	3/62	9/39
Han [11], 2022	22/271	0/0	0/271	0/0	5/266	0/0	0/0
Borghammar [40], 2022	0/55	0/0	0/55	0/0	NR	NR	NR

NR: Not reported or unclear; MacroA: Macroadenoma; Endocrinopat: Endocrinopathies.

with an associated I^2 of 66 %. Using the 2017 WHO classification of pituitary adenomas including immunohistochemistry and transcription factor analysis, Lenders et al. classified 111 NFPTs into more than 10 different subtypes [8], and thus highlighting that NFPTs are likely to have a different prognosis and growth pattern contributing to the observed heterogeneity. The risk of growth in microadenomas was estimated to 1.8/100 PYs among 675 patients in the current study. Removing one study [30], the estimate was reduced to 1.6/100 PYs providing a solid estimate based on individual patient data and low to moderate heterogeneity. The study by Sam et al. [30] did exclude patients who had less than a year of follow-up, which may imply that smaller microadenomas were excluded thus enriching the cohort with more severe cases. Compared to the systematic review performed by Fernandez-Balsell et al. in 2010 [1], the current findings suggest lower incidence rates of growth for both micro- and macroadenomas. Removing one outlier [30], the risk of tumor regression was estimated to 3.7/100 PYs (▶ **Table 3**), which may reflect either that the most prevalent definition of a significant tumor change of 2 mm may be too small causing uncertain estimates or that tumor regression is a common event.

▶ **Table 3** Incidence of events during follow-up in conservatively treated non-functioning pituitary tumors.

	Events/total (%)	Studies n	Range of events//100 PYs	Incidence/100 PYs[1] (95% CI; I^2)
Tumor growth				
Overall	421/1914 (22.0)	28	0 to 14.2	I^2 = 90%
Macroadenomas	201/510 (39.4)	19	0 to 19.5	I^2 = 82%
Microadenomas	57/675 (8.4)	15	0 to 12.2 (0 to 7.7)[2]	1.8 (0.9 to 2.8; 58%)
New endocrinopathies				
Overall	40/1007 (4.0)	12	0 to 2.3	0.9 (0.5 to 1.2; 35%)
Macroadenomas	27/382 (7.1)	9	0 to 4.5	1.5 (0.9 to 2.1; 0%)
Microadenomas	11/277 (4.0)	6	0 to 3.8	0.7 (0.0 to 1.6; 37%)
Need for active treatment				
Overall	119/1603 (7.4)	21	0 to 7.7	I^2 = 80%
Macroadenomas	101/640 (15.8)	18	0 to 8.9	3.1 (2.1 to 4.1; 52%)
Microadenomas	19/673 (2.8)	13	0 to 11.5 (0 to 4.5)[3]	0.5 (0.1 to 0.9; 37%)
Recovery of endocrinopathy				
Overall	14/264 (5.3)	3	0.5 to 3.5	1.2 (0.1 to 2.3; 60%)
New visual defects				
Overall	70/992 (7.1)	18	0 to 9.8	I^2 = 78%
Macroadenomas	69/517 (13.3)	13	0 to 10	2.6 (1.5 to 3.8; 65%)
Microadenomas	1/403 (0.2)	8	0 to 3.7	0.1 (0.0 to 0.3; 0%)
Pituitary apoplexy				
Overall	21/826 (2.5%)	10	0 to 3.4	0.4 (0.1 to 0.7; 23%)
Tumor shrinkage				
Overall	248/1619 (15.3%)	20	1.3 to 19.7 (1.3 to 7.8)[4]	I^2 = 80%

[1] Incidence per 100 person years is based on a random effects meta-analysis. Estimate is only calculated if $I^2 \leq 75\%$. [2] One outlier removed, Sam et al. [30], changing the estimate to 1.6/100 PYs (95% CI. 0.8 to 2.4; I^2 = 49%) [3] One outlier removed, Arita et al. [21], changing the estimate to 0.4/100 PYs (95% Cl. 0.1 to 0.8; I^2 = 32%) [4] One outlier removed, Carsote et al. [24], changing the estimate to 3.7/100 PYs (95% Cl. 2.6 to 4.7; I^2 = 74%) PYs: Person years.

The overall risk of developing a new endocrinopathy was estimated to 0.9/100 PYs, an estimate associated with an I^2 of 35%. Separate analysis of micro- and macroadenomas suggested that new endocrinopathies occurred twice as frequently in macroadenomas compared to microadenomas with incidence rates of 1.5/100 PYs and 0.7/100 PYs, respectively. However, in the subgroup analysis of studies reporting on both micro- and macroadenomas, the difference was not significant. These estimates are much lower than previously reported by Fernandez-Balsell reporting an incidence of 11.9/100 PYs and 4.0/100 PYs for macro- and microadenomas [1]. Theses discrepancies were not explained by time of publication, however, only three of 12 studies included on this outcome were published prior to 2011 and included in the work by Fernandez-Balsell et al. [1] and the observed variations may be explained partly by chance.

The risk of undergoing active treatment, that is, surgery, was estimated to 3.1/100 PYs in macroadenomas and 0.4/100 PYs in microadenomas, both estimates were associated with small to medium heterogeneity. This is an obvious important outcome and to our knowledge this is the first time for a systematic review to report on this outcome. As described previously [3] surgery may be performed due to chiasma pressure or for recovery of pituitary function, with the later not being practiced all places, which may contribute to the differences in estimates.

Secondary outcomes

Tumor shrinkage was reported with an incidence of 3.7/100 PYs and in comparison, the risk of growth was 1.8/100 PYs in microadenomas. Pituitary apoplexies are often associated with shrinkage of tumor size; however, this was only observed in 0.4/100 PYs and is unlikely to explain the high incidence of tumor shrinkage. The definition of shrinkage was rarely reported, and it is possible that studies using as little as 1 or 2 mm as cut offs for growth or shrinkage may report higher incidence of change in tumor size due to misreading.

Perspectives

Guidelines from the Endocrine Society on pituitary incidentalomas recommend that microadenomas should have a repeat MRI-scan after 1 year, and if the incidentaloma does not change in size, then every 1–2 years the following three years and subsequently with gradually less frequency [40]. With stable size of the microadenoma,

regular endocrine assessment is not recommended, reflecting the association between tumor size and risk of pituitary endocrine failure. The current findings strongly support differentiated follow-up of patients with microadenomas compared to macroadenomas. Clinically relevant growth in microadenomas is rare and resources should primarily be allocated to follow-up of macroadenomas with higher risk of growth, surgery and failure of endocrine function. Predicting growth behavior in NFPTs prior to pathological classification remains primarily based on tumor size and tumor behavior in terms of aggressiveness and invasiveness. The current systematic review identifies a low risk of growth, low risk of new endocrinopathies and low risk of surgical interventions in patients with microadenomas and we suggest that patients with normal endocrine function at baseline and no signs of tumor growth at a two- or three-year MRI follow-up could end any further assessment of pituitary function or size. This would apply to well informed patients that would be able to respond to symptoms associated with tumor growth, that is, visual disturbances or failure of pituitary function, while less able patients may remain under some sort of endocrine observation.

Conclusion

The risk of growth in NFPTs is lower than previously reported. In particular, the low risk of growth, new endocrine failure, or need for surgery is low in microadenomas calling for shorter duration of follow-up than suggested by current guidelines. Future studies with long follow-up and detailed description of endocrine function and tumor characteristics are currently warranted in order to improve pre-surgical/pre-pathological guidance on the risk of clinically relevant outcomes, especially for macroadenomas.

Conflict of Interest

The authors declare that they have no conflict of interest.

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