ORIGINAL RESEARCH

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Long-Term Changes in the Size of Pituitary Microadenomas

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Background: The estimated prevalence of pituitary lesions is 10% to 38.5% in radiologic studies. However, how frequently these incidental lesions should be monitored by serial pituitary magnetic resonance imaging (MRI) remains unclear.

Objective: To evaluate changes in pituitary microadenomas over time.

Design: Retrospective, longitudinal cohort study.

Setting: Mass General Brigham, Boston, Massachusetts.

Patients: Evidence of pituitary microadenoma from MRI.

Measurements: Dimensions of pituitary microadenomas.

Results: During the study period (from 2003 to 2021), 414 patients with pituitary microadenomas were identified. Of the 177 patients who had more than 1 MRI, 78 had no change in the size of the microadenoma over time, 49 had an increase in size, 34 had a decrease in size, and 16 had both an increase and decrease in size. By linear mixed model analysis, the estimated slope was 0.016 mm/y (95% CI, −0.037 to 0.069). In the subgroup analysis, pituitary adenomas with a baseline size of 4 mm or less tended to increase in size. The estimated slope was 0.09 mm/y (CI, 0.020 to 0.161). In contrast, in the subgroup with baseline tumor size greater than 4 mm, the size tended to decrease. The estimated slope was −0.063 mm/y (CI, −0.141 to 0.015).

Limitation: Retrospective cohort, some patients were lost to follow-up for unknown reasons, and data were limited to local large institutions.

Conclusion: During the study period, approximately two thirds of the microadenomas remained unchanged or decreased in size. The growth, if any, was slow. These findings suggest that less frequent pituitary MRI surveillance for patients with incidental pituitary microadenomas may be safe.

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Incidental pituitary lesions are common and have been estimated to occur in approximately 11% to 23% of the population in postmortem studies (1, 2). In radiologic studies of the head, the estimated prevalence of pituitary adenomas has been reported as 10% to 38.5% (3–7). With increased use of brain imaging techniques, more pituitary lesions have been identified. Asymptomatic solid and/or cystic lesions are often described as incidentalomas. These lesions are categorized as macro- versus microadenomas, using a 10-mm maximal diameter as the cutoff. Most pituitary incidentalomas are microadenomas (2). In 2011, the Endocrine Society published guidelines for following incidental pituitary lesions (8). This guideline recommends pituitary magnetic resonance imaging (MRI) 1 year after the initial diagnosis, and then every 1 to 2 years for the next 3 years. If the adenoma remains stable during this time, the guidelines indicate that monitoring can then be done less frequently thereafter (8). However, limited studies have evaluated dynamic changes over time in pituitary incidentalomas (9–11). Understanding the behavior of pituitary microadenomas provides improved clinical guidance for cost-effective management of these pituitary incidentalomas.

Methods

In this retrospective cohort study, patients with pituitary microadenomas were found from our institution's database between November 2003 to March 2021 using a Research Patient Data Registry (RPDR) search followed by chart review. Inclusion criteria were MRI of the pituitary with or without contrast in the RPDR search and keyword search for "pituitary microadenoma" and "pituitary lesion" in progress notes. Exclusion criteria in the RPDR search were prolactin level = high and exposure to cabergoline and/or bromocriptine. The RPDR is a centralized clinical data registry, or data warehouse. It contains data from several source systems, including data from the Mass General Brigham Clinical Data Repository and from Epic at Brigham and Women's Hospital, Massachusetts General Hospital, and other hospitals associated with Mass General Brigham. We reviewed medical records to confirm the diagnosis and to collect data, including patient demographic characteristics, medications, and pituitary imaging findings. We define the first MRI as the first available MRI in the study period (2003 to 2021) and the last MRI as the last available MRI in the study period for each patient.

There were 2109 patients identified by the RPDR search. After medical record review, 1561 patients were excluded because of a lack of a recorded or confirmed diagnosis of pituitary microadenoma (**Figure 1**). Because of limitations of the RPDR search tool, we were unable to completely exclude all patients treated with dopamine agonists and patients treated with somatostatin analogues and/or growth hormone antagonist through the RPDR search. Therefore, any remaining patients treated with dopamine agonists ($n = 112$), somatostatin analogues, and/or growth hormone antagonist ($n = 22$) were identified and excluded during the medical record review (**Figure 1**). We did not entirely exclude functioning adenomas. However, in this cohort, the adenomas were largely nonfunctioning adenomas (after excluding prolactinomas and patients treated with dopamine agonists,

somatostatin receptor ligands, or growth hormone antagonist).

Patients with a diagnosis of pituitary microadenoma (tumor size ≤10 mm) were included in this study. Patients with only 1 brain MRI study ($n = 237$) were included to compare baseline characteristics. Patients with more than 1 MRI ($n = 177$) had further analyses. Tumor size was recorded by reviewing the MRI reports. The tumor size is represented as the largest dimension measured in each report, or by the reported dimension if 3 dimensional measurements were not available. We used the largest dimension rather than tumor volume because not all lesions were reported with measurements of all 3 dimensions.

Statistical Analyses

Statistical analyses were done using SAS, version 9.4 (SAS Institute). Continuous data were presented as median (95% CI). We did a mixed model analysis to find the group mean trajectory for the cohort over the study period since the initial MRI. We tested different forms of years since the initial MRI and kept only the linear term in the final model because adding other terms did not improve the goodness of fit. Both individual intercept and slope were included as random effects. We did a subgroup analysis to compare patients with pituitary microadenomas sized 4 mm or less and greater than 4 mm. We used 4 mm as the cutoff because the median tumor size was 4 mm.

Role of the Funding Source

No funding was received for this study.

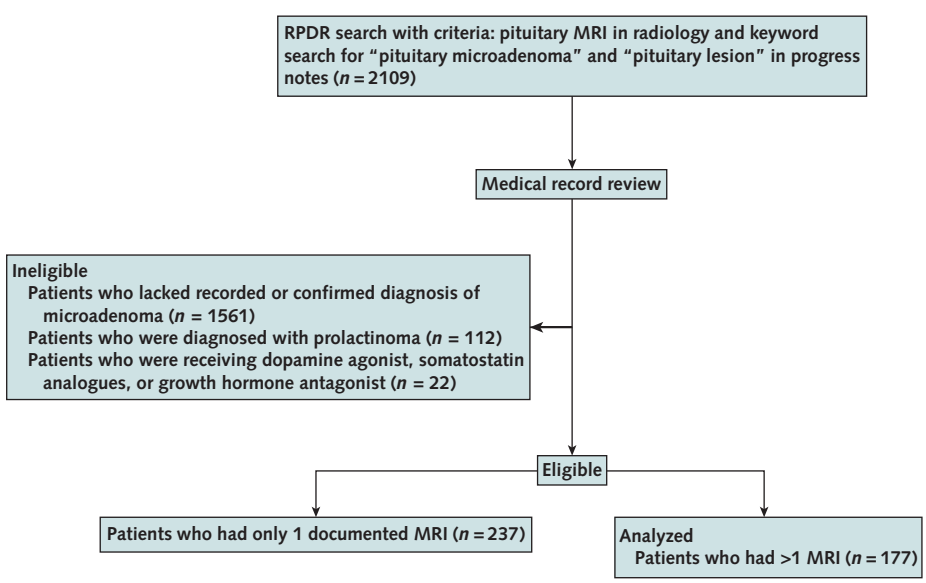
RESULTS

A total of 414 patients with a diagnosis of pituitary microadenoma had at least 1 brain MRI done during the study period. Of these, 43% had more than 1 MRI. The median ages at the time of the initial MRI in patients with 1 or more than 1 MRI were 45 and 42 years, respectively. The median maximal tumor size was 4 mm in patients with 1 MRI and with more than 1 MRI, respectively (**Appendix Table**, available at Annals.org). Demographic data for the 177 patients with more than 1 MRI are outlined in the **Table**. During the study period, 63% of microadenomas remained unchanged (44%) or decreased (19%) in size, whereas 28% increased in size. In this cohort study, 72.3% of patients were women. Among the 10 patients who had tumor resection, there were 5 corticotroph adenomas, 1 somatotroph adenoma, 1 Rathke cleft cyst, and 3 with only anterior pituitary tissue. The indications for tumor resection were Cushing syndrome ($n = 5$), acromegaly ($n = 1$), hypogonadism ($n = 1$), intractable headache ($n = 1$), and unknown reasons ($n = 2$). The median follow-up was 4.91 years (95% CI, 3.88 to 5.32 years).

We did a mixed model linear regression analysis to determine the overall trajectory for each patient as well as for the overall cohort. **Figure 2** presents raw individual trajectories together with the fitted group mean trajectory and 95% CI. For the individual trajectories, there were many patterns of microadenoma size change: unchanged, increased, decreased, increased followed by unchanged, decreased followed by unchanged, increased followed by decreased, and decreased followed by increased. Among all patients, the estimated slope was 0.016 mm/y (CI, −0.037 to 0.069) by mixed model analysis (**Figure 2**).

We did a subgroup analysis to compare patients with a baseline tumor size of 4 mm or less and those with a baseline tumor size of greater than 4 mm. In patients with a baseline tumor size of 4 mm or less, the size tended to increase. The estimated slope was 0.09 mm/y (CI, 0.020 to 0.161) (**Figure 3**, *left*). In patients with a baseline tumor size greater than 4 mm, the size tended to decrease. The

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram.



MRI = magnetic resonance imaging; RPDR = Research Patient Data Registry.

Table. Demographic Data

Demographic Characteristic	Total	Men	Women
Patients, *n* (%)	177 (100)	49 (27.7)	128 (72.3)
Median age at diagnosis (95% CI), *y*	42.1 (39.5–45.6)	47.7 (36.7–51.8)	41.6 (38.6–44.5)
Median diameter of tumor on MRI at baseline (95% CI), *mm*	4.0 (4.0–5.0)	4.0 (3.0–5.0)	4.0 (4.0–5.0)
Tumor size, *n* (%)			
Unchanged	78 (44.1)	25 (51.0)	53 (41.4)
Increased	49 (27.7)	14 (28.6)	35 (27.3)
Decreased	34 (19.2)	6 (12.2)	28 (21.9)
Increase and decrease	16 (9.0)	4 (8.2)	12 (9.4)
Had tumor resection, *n* (%)	10 (5.6)	3 (6.1)	7 (5.5)

MRI = magnetic resonance imaging.

estimated slope was −0.063 mm/y (CI, −0.141 to 0.015) (Figure 3, *right*).

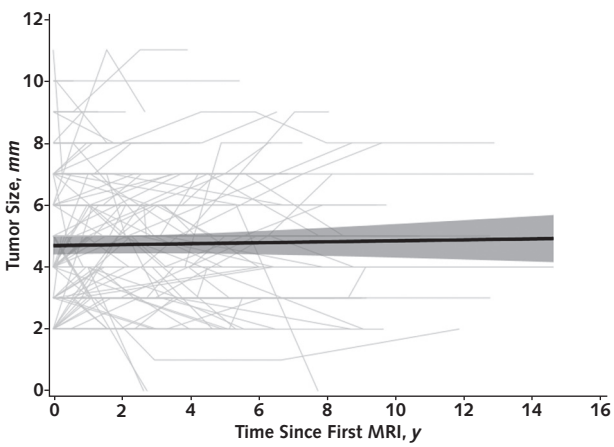
DISCUSSION

In this study, we evaluated changes in size on the basis of radiographic imaging (MRI) of pituitary microadenomas in 177 patients over a 17-year period (2003 to 2021), with a median follow-up of 4.91 years. We defined the initial MRI as the first MRI in the study period. Although it is possible that a few patients may have had MRI scans before 2003, the lack of inclusion of MRI data before 2003 should not affect study outcomes because the aim of this study was to investigate the dynamic changes in tumor size over our study period.

In our cohort, there were 237 patients with only 1 brain MRI (Figure 1). We compared the baseline characteristics (age, sex, and tumor size) of these 237 patients with the 177 patients with more than 1 MRI. We found that the 2 groups shared similar demographic characteristics (Appendix Table).

With an average of 3.76 MRI records per microadenoma, we found that 28% of the microadenomas increased in size over the study period. The patients with microadenomas that increased in size over the study period had more frequent MRIs, with an average of 4.1 records per microadenoma. More than half (63%) of the microadenomas were either unchanged (44%) or decreased (19%) in size during the study period (Table). The remaining 9% showed an increase followed by a decrease in size. In a prior study, the incidence of nonfunctioning pituitary adenoma enlargement was 20% (23 of 115) during a mean follow-up of 4.2 years (range, 0.5 to 14.4 years) (10). However, in this prior study, the authors did not subcategorize micro- or macroadenomas. Another study showed that 3.2% of microadenomas had a size increase within a 5-year follow-up period (11). In our study, the incidence of size increase in microadenomas seems to have been relatively higher. However, given the varied study designs and durations, it is difficult to draw a definitive conclusion that the occurrence of tumor growth was higher in our study. In a previous meta-analysis, the incidence of tumor growth in pituitary microadenomas was reported to be 3.3% per year (9). We believe it is important to assess the risks for microadenoma growth. However, in our cohort, we did not calculate the yearly incidence of tumor growth because of the varied study duration for each patient.

Figure 2. Mixed model analysis of cohort.



The *y*-axis represents the size of each microadenoma in millimeters. The *x*-axis represents the time (in years from diagnosis) since the tumor size was recorded. Each gray line represents the trajectory of each patient. The black line and gray band represent the mean trajectory and 95% CI of the entire cohort. MRI = magnetic resonance imaging.

In a mixed model analysis of all patients, the mean trajectory of the cohort displayed a tendency for a slight increase in size, with an estimated slope of 0.016 mm/y (CI, −0.037 to 0.069) (Figure 2). However, the trajectories for individual persons were diverse, with the change in size ranging from increased, unchanged, or decreased. The tumor size over the study period was between 0 and 12 mm. Few microadenomas progressed to macroadenomas over the study period. Among the 28% of microadenomas that increased in size, the maximal size increase was 6 mm. Our findings suggest that although a subgroup of patients displayed an increase in tumor size over the study period, the tumor growth rates were slow and the increases in size were limited.

Over the study period, 1.7% of the microadenomas progressed to macroadenomas (>10 mm) (Figure 2). An increase in the size of a pituitary microadenoma to greater than 1 cm (macroadenoma) is concerning. We did a subgroup mixed model analysis to evaluate the association between microadenoma size and risk for tumor growth. We hypothesized that larger microadenomas would be associated with a higher tendency for tumor enlargement. In our subgroup analysis, the microadenomas with a baseline size

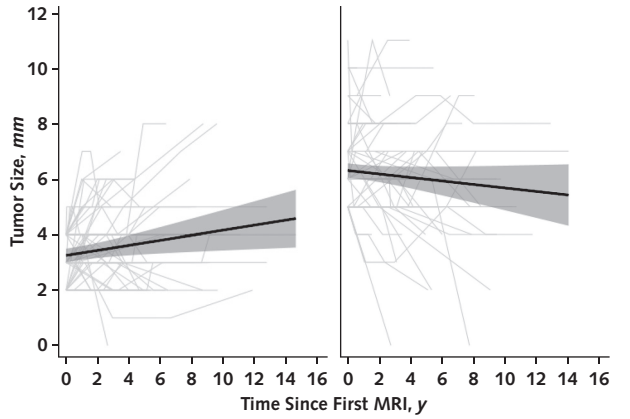
of 4 mm or less tended to increase in size (**Figure 3**, *left*). In contrast, microadenomas with a baseline size of greater than 4 mm tended to decrease in size (**Figure 3**, *right*). These findings could originate from measurement error of tumor size and subsequent regression toward the mean and are compatible with the conclusion that, among microadenomas, the risk for tumor growth does not seem to be strongly associated with tumor size. However, as we were unable to identify specific clinical features that lead to more clinically significant growth in the small proportion of patients with microadenomas that progressed to macroadenomas, future study is certainly indicated.

During our study period, 10 patients (5.6%) had pituitary tumor resection. The resected microadenomas were mostly functioning. The findings show that most pituitary microadenomas retained long-term stability, avoiding the need for surgical intervention. The growth pattern of pituitary microadenomas was different from that of nonfunctioning pituitary adenomas after radiotherapy (12) and of postoperative residual nonfunctioning pituitary tumors treated with dopamine agonists (13). Pituitary lesions include both cystic and solid lesions. The current Endocrine Society guidelines do not recommend any differences in MRI follow-up for these 2 types of pituitary lesions (8). Therefore, we did not do a subgroup analysis on solid and cystic lesions. However, characterizing the growth patterns of solid versus cystic pituitary lesions would be important in a future study.

In 2011, the Endocrine Society published a clinical practice guideline for the evaluation and management of pituitary incidentalomas (8). These recommendations were based on the results of a meta-analysis (9). There have been no updated guidelines in the past decade, likely because of the paucity of new studies in this field. Our study provides new data to help understand the natural progression of pituitary microadenomas. Our data suggest that, among patients with incidentalomas that demonstrate growth, the growth rate is generally slow. On the basis of these findings, we recommend increasing the time interval between pituitary MRIs in most patients with pituitary incidentalomas. In addition, our subgroup analysis showed that among pituitary microadenomas, a larger initial tumor size was not associated with the risk for tumor progression. Therefore, there is no indication to perform more frequent pituitary MRIs in patients with an initial larger-sized adenoma if the size is 10 mm or less.

Furthermore, we have shown in our demographic data that the median age of patients in this cohort was 44 years (**Appendix Table**). The long-term consequences of frequent exposure to intravenous gadolinium in this age group is not known but is receiving increasing attention and concern. The optimal assessment of sellar and suprasellar mass lesions by pituitary MRI requires both noncontrast and gadolinium-enhanced MRI imaging (14). Although gadolinium-based contrast agents are usually well tolerated, their use is associated with rare allergic reactions, gadolinium deposition, and nephrogenic systemic sclerosis in patients with impaired renal function (15). Accumulating evidence has shown the deposition of gadolinium in the deep nuclei of the brain even in patients with normal renal function, particularly after repeated exposure to gadolinium-based contrast agents (16–19). Although there are no reliable data about its clinical or biological significance (16, 18, 20), the potential for gadolinium deposition in the brain is potentially concerning.

Figure 3. Mixed model analysis by subgroup based on initial tumor size.



The *y*-axis represents the size of each microadenoma in millimeters. The *x*-axis represents the time (years from diagnosis) since the tumor size was recorded. Each gray line represents the trajectory of each patient. The black line and gray band represent the mean trajectory and 95% CI of each subgroup. MRI = magnetic resonance imaging. **Left.** Patients with initial tumor size ≤4 mm. **Right.** Patients with initial tumor size >4 mm.

Although several previous studies evaluated the hormonal status among patients with incidental pituitary adenomas (9, 21), in this study we did not analyze hormone levels because our primary focus was on changes in size of pituitary adenomas. To eliminate the effect of medical treatments on tumor growth, we excluded prolactinomas and patients treated with dopamine agonists, somatostatin analogues, or growth hormone antagonist.

In our cohort, there were more women (72%) than men (28%). The cause of this disproportionate distribution of sex in our study is unclear. In an earlier study, the female-to-male sex ratio varied by adenoma type and the age of the patient (22). However, this study did not report adenoma size. In another study including 27 patients with pituitary adenomas, 25 had macroadenomas (23). The ratio of women to men in this study was 1:1.5. The men were older.

One limitation of this study is its retrospective design. Another limitation is the variability of the MRI study interval and the duration of follow-up. The variability of the MRI study interval and follow-up duration could have affected the estimated changes in microadenoma size. We also did not have access to information regarding the reasons that some patients were lost to follow-up. Future prospective studies will help to address many of the limitations associated with such a retrospective cohort study. This study was done in a single local institution. Further multicenter studies to assess changes in microadenomas in more diverse populations are indicated. Finally, although

this study focused on changes in adenoma size, assessment of pituitary function in future studies would be important.

In conclusion, our study systematically assessed dynamic changes in size of pituitary microadenomas in 177 patients. In this study, approximately a third of microadenomas increased in size over the follow-up period. Among the microadenomas that grew, the growth rate was slow, with a maximal size less than 12 mm and only a small percentage (1.7%) of microadenomas progressing to macroadenomas over the study period. The initial tumor size was not associated with a higher likelihood of tumor progression. These findings suggest that less frequent pituitary MRI surveillance for patients with incidental pituitary microadenomas may be safe. We recommend repeating a pituitary MRI 1 year after the initial MRI. If there is no change in the pituitary lesion, we recommend that the next MRI be done 3 years after the second MRI. If the lesion again remains unchanged, we suggest repeating the pituitary MRI every 5 years, or sooner if the patient develops severe headaches or changes in peripheral vision.

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Reproducible Research Statement: *Study protocol:* Available from Dr. Min (e-mail, lmin@bwh.harvard.edu). *Statistical code and data set:* Not available.

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Appendix Table. Comparison of Demographic Characteristics of Patients Included in the Study With Those Excluded Because They Had Only 1 Documented MRI

Demographic Characteristic	Total	Multiple MRIs	One MRI
Patients, *n*	414	177	237
Median age at diagnosis (95% CI), *y*	43.6 (42.0–45.2)	42.1 (39.5–45.6)	44.6 (42.3–46.9)
Men, *n*	117	49	68
Women, *n*	297	128	169
Median maximum tumor size (95% CI), *mm*	4.0 (3.7–4.3)	4.0 (4.0–5.0)	4.0 (3.5–4.5)

MRI = magnetic resonance imaging.