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RESEARCH

A multicenter study of clinical outcomes and volumetric trends in suspected microprolactinomas

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Abstract

The diagnosis of pituitary microprolactinomas is often obscured by relatively low levels of elevated prolactin compared to macroprolactinomas. This may lead to varying patterns of medical therapy versus observation. We sought to correlate prolactin levels in suspected microprolactinomas with tumor volumes and clinical outcomes. This was a multicenter retrospective study of patients with pituitary microadenomas with baseline prolactin levels > 18ng/ml for males and > 30ng/ml for females. A linear-mixed model was used to depict changes in tumor volume over time. There were 65 patients with a mean tumor volume of 95.9mm^3 and mean prolactin level of 59.4ng/ml. There were significantly higher prolactin levels in patients with tumors above the mean volume versus below (74.0 versus 53.4ng/ml, $p = 0.027$). 26 patients were observed, 31 were treated with anti-dopaminergic therapy, and 8 had surgery. There were significantly greater baseline prolactin levels for patients who were treated surgically (mean 86.4ng/ml) than those treated medically (mean 61.7 g/ml) or observed (mean 48.5ng/ml) ($p = 0.02$). Among the 26 patients who were surveilled, 13 patients demonstrated spontaneous tumor shrinkage, 12 remained stable, and 1 patient's tumor grew but was lost to follow-up. Linear mixed modeling demonstrated a statistically significant rate of tumor shrinkage over time of 3.67mm^3/year ($p = 0.03$). When analyzing patients who were observed versus those requiring surgery after initially being surveilled, there were significantly greater baseline PRL/volume ratios in surgical patients versus those observed (8.1 ng/ml/mm^3 versus 2.4 ng/ml/mm^3, $p = 0.025$). Suspected microprolactinomas may demonstrate more convincingly elevated prolactin levels when measuring over 95.9mm^3. Tumors with baseline prolactin levels over 50ng/ml may be more inclined to undergo medical treatment. In tumors with levels below 50ng/ml, it may be reasonable to undergo surveillance as these tumors tend to spontaneously shrink over time. In tumors that are surveilled, an elevated baseline PRL/volume ratio of > 8 ng/ml/mm^3 may be indicate serial tumor growth that may necessitate medical and/or surgical intervention.

Keywords Pituitary · Prolactinoma · Microadenoma · Prolactin

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Introduction

Prolactinomas are the most common pituitary adenomas (approximately 40%) and make up the vast majority of hormonally functional pituitary adenomas [1]. Clinically, patients typically present with galactorrhea, menstrual irregularities, loss of libido and/or infertility, as well as sexual dysfunction and hypogonadism particularly in men. Larger tumors may also cause headaches, visual field deficits, and hypopituitarism [2]. First-line treatment for prolactinomas remains dopamine agonists, which have been shown to shrink tumors and restore gonadal function with concomitant decrease in prolactin (PRL) levels. In patients with tumors that are resistant to dopamine agonists, surgical resection is recommended.

Non-functioning pituitary adenomas are commonly an incidental finding on imaging, obtained to work-up other symptoms. Compared to macroadenomas, microadenomas of this type are more likely to remain stable or decrease in size with long-term follow-up [3]. Of note, guidelines released by the Endocrine Society state that asymptomatic patients with microprolactinomas do not necessarily require treatment upfront, given that a natural history study of untreated hyperprolactinemia, albeit decades old, found that these tumors were unlikely to grow [4, 5]. In addition, hypogonadal premenopausal women may also be treated with oral contraceptives in lieu of dopamine agonists [4].

Previous studies have suggested that prolactin levels correlate with tumor size. That said, these studies have typically looked at a wide range of tumor volumes [6–8]. However, in cases of small tumors, the diagnosis of a pituitary microprolactinoma is often obscured by relatively low levels of elevated prolactin compared to macroprolactinomas, and patients may not always exhibit classical symptoms of hyperprolactinemia. As a result, in cases of microprolactinomas, there may be varying patterns of management, ranging from initiating medical therapy, considering surgery, or observation.

In this study, we sought to correlate baseline prolactin levels with tumor volumes in suspected microprolactinomas. We also compared baseline prolactin levels and volumes amongst patients who were managed with medical therapy, surgery, or observation.

Materials and methods

This was a multicenter retrospective study of patients with pituitary microadenomas with baseline prolactin levels > 18ng/ml for males and > 30ng/ml for females. Data collected included basic patient demographics, presenting symptoms, relevant endocrine laboratory values, radiographic findings on initial and subsequent MRI, and clinical outcomes. Inclusion criteria for a microadenoma were tumors that measured under 10 mm in greatest single dimension. Subsequently, tumor volumes were calculated via the ABC/2 formula, approximating the lesion shape as an ellipsoid. This study was conducted under an institutional board approved protocol.

To analyze the data, we employed a linear mixed-effects model, which allowed us to account for the correlation between repeated measurements taken from the same patient. The analysis was performed using Julia (v1.9.1) programming language, specifically employing the MixedModels.jl package. The model was formulated as follows:

$$\text{Volume} \sim \text{Time} + (1 + \text{Time} \mid \text{PatientID}).$$

In this model, the response variable volume represents the tumor volume, while time is the fixed effect representing the number of days between consecutive MRI scans. To account for the variability and correlation in tumor growth rates across patients, we included a random intercept and a random slope for time within patientID. This random effects structure allows each patient to have a unique baseline tumor volume and a unique tumor growth rate over time. By employing this approach, we were able to assess the overall trend in tumor growth while also considering the variability among individual patients.

To quantify the uncertainty in our predictions and obtain robust estimates of the confidence intervals for the fixed-effect coefficients, we employed a bootstrapping approach. Bootstrapping is a resampling technique that involves repeatedly drawing random samples from the dataset (with replacement) and recalculating the estimates on each sample. We performed bootstrapping with 1,000 iterations which enabled us to estimate the variability in our predictions and provided 95% confidence intervals around the estimated tumor volumes over time.

Results

There were 65 patients (18 male, 47 female; mean age 44 years, range: 15–74 years). At time of diagnosis, mean tumor volume was 95.9 mm^3 (SD: 114.2 mm^3, range: 4-500 mm^3), and mean prolactin level was 59.4 ng/ml (SD: 34.4 ng/ml, range: 19.1–170 ng/ml). The mean follow-up duration as measured from time of first MRI to the last scan was 85.1 months (SD: 56.8 months) and the mean number of MRI scans obtained was 4.3 (SD: 1.9). When analyzing the whole cohort, there was no significant correlation between prolactin levels and tumor volume at diagnosis (Pearson $R = 0.09, p = 0.47$). Upon sub-group analysis of patients with tumor volumes above ($n = 19$) and below ($n = 46$) the mean, there were significantly higher

Table 1 Patient demographic data

Variable	
Total (n)	65
Male sex (n)	18
Average age (years)	44
Mean follow-up (months)	85.1
Mean # of MRI scans (n)	4.3
Treatment modality	
Observation (n)	26
Surgery alone (n)	4
Surgery after failing medical therapy (n)	4
Medical therapy (n)	31
Presenting Symptoms	
Menstrual irregularities (n)	17
Hypogonadal symptoms (n)	12
Galactorrhea (n)	5
Asymptomatic (n)	29

prolactin levels in patients with tumors above the mean volume of 95.9mm^3 versus below (74.0 versus 53.4ng/ml,95% CI 2.432–38.8,$p=0.027$).

26 patients were observed, 31 were treated with dopaminergic therapy, and 8 had surgery (4 had surgery after failing medical therapy). They presented with the following symptoms. Among the 26 patients who were observed, 11 had mild menstrual irregularities, 2 had hypogonadal symptoms, and the rest were asymptomatic. Among the 31 patients who were treated with anti-dopaminergic therapy, 8 had hypogonadal symptoms, 5 had galactorrhea, 4 had menstrual irregularities, and the rest were asymptomatic. Among the 8 patients who had surgery, 2 had menstrual irregularities, 2 had hypogonadism, and the rest were asymptomatic. Three of the 8 patients had histopathological diagnosis of a prolactinoma, while the remaining patients were found to have a corticotroph adenomas ($n=2$), non-functioning adenomas ($n=2$), and mixed corticotroph and gonadotroph adenoma ($n=1$). These demographic data are presented in Table 1.

There were significantly greater baseline prolactin levels for patients who treated surgically (mean: 86.4 ng/ml, SD: 39.6 ng/ml) than those treated medically (mean 61.7 ng/ml, SD: 38.2 ng/ml), or were observed (mean 48.5 ng/ml, SD: 22.0 ng/ml) ($p=0.02$; $F=4.2$; $R^2=0.12$). However, there were no significant differences in baseline volumes for patients treated surgically (mean 120.0 mm^3, SD: 122.4 mm^3), medically (mean 111.2mm^3, SD: 118.2 mm^3), or observed (mean 70.24 mm^3, SD: 106.1 mm^3) ($p=0.33$; $F=1.1$; $R^2=0.04$). Among surgically treated patients, there were no significant differences in baseline prolactin levels for patients with histopathologically diagnosed prolactinomas (mean 80.2 ng/ml, SD: 37.5 ng/ml) versus other histologies (90.1 ng/ml, SD: 44.6 ng/ml) ($p=0.76$; $F=1.4$; $R^2=0.02$).

Among the 26 patients who were surveilled, 13 patients demonstrated spontaneous tumor shrinkage, 12 remained stable, and 1 patient's tumor grew but was lost to follow-up. Linear mixed modeling demonstrated a statistically significant rate of tumor shrinkage over time of 3.67mm^3/year ($p=0.03$) (Fig. 1). There were no significant differences in baseline prolactin in patients whose tumors spontaneously shrunk (mean 46.1 ng/ml, SD: 22.3 ng/ml) versus remained stable (mean 52.3 ng/ml, SD: 22.7 ng/ml) (95% CI:-12.4-24.9, $p=0.50$). Likewise, there were no significant differences in baseline volumes (mean 56.2mm^3, SD: 65.1 mm^3

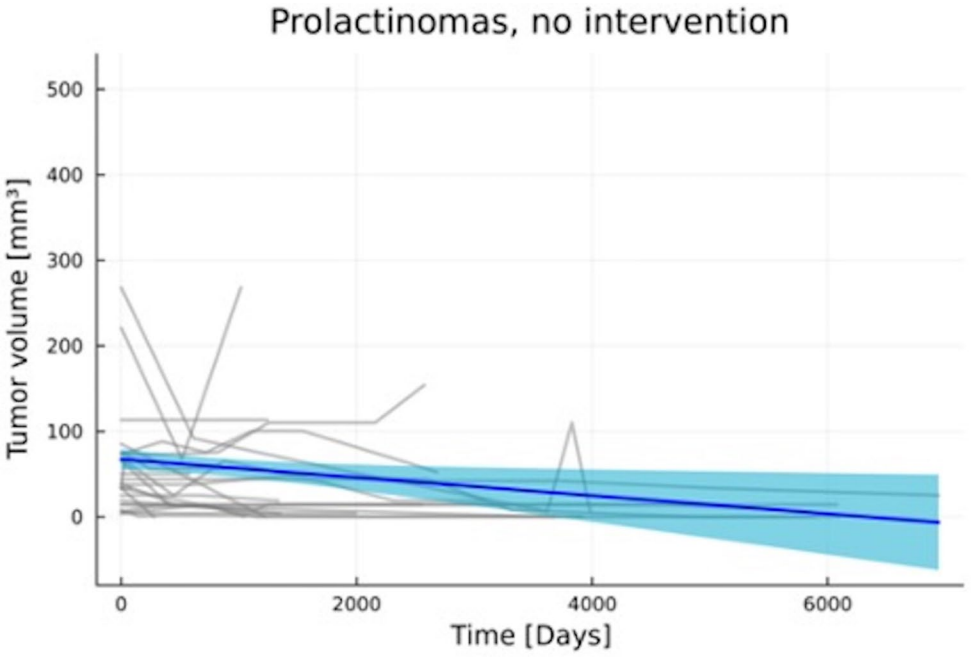

Fig. 1 Mixed model analysis of patients with microprolactinomas who were observed without any intervention. The x-axis demonstrates time in days from diagnosis since tumor size was recorded. The y-axis demonstrates changes in tumor volume over time in mm^3. Each gray line represents the trajectory of each patient. The blue line and light blue band represent the mean trajectory and 95% CI of the entire cohort

versus 91.0 mm^3, SD 140.9 mm^3 respectively) (95% CI: 54.8-124.4, $p = 0.43$).

A baseline PRL/volume ratio metric was then explored to predict clinical outcomes. When analyzing patients who were observed versus those requiring surgery after initially being surveilled, there were significantly greater baseline PRL/volume ratios in surgical patients versus those observed (8.1 ng/ml/mm^3 versus 2.4 ng/ml/mm^3, 95% CI:0.80–10.7, $p = 0.025$). However, PRL/volume ratio did not predict patterns of medical treatment failure for patients successfully managed with medical treatment versus those who failed and required surgery (2.25 ng/ml/mm^3 versus 0.91 ng/ml/mm^3, 95% CI:-7.7-5.03, $p = 0.67$). Likewise, among surgically treated patients, there were no significant differences in baseline PRL/volume ratios for patients with histopathologically diagnosed prolactinomas versus other histologies (3.0 ng/ml/mm^3 versus 5.4 ng/ml/mm^3, 95% CI:-13.9-18.7, $p = 0.73$).

Discussion

In this study, we studied relationships between baseline prolactin levels and volumes of suspected microprolactinomas in 65 patients with > 1 MRI over an average follow-up period of 7 years. We found significantly elevated baseline prolactin levels for patients with tumor volumes above the mean cohort volume, compared to below. Likewise, patients with greater baseline prolactin levels and PRL/volume ratios were more likely to require surgery and/or medical treatment versus those who were observed. We also found a significant rate of tumor shrinkage over time in the tumors of patients that were observed who also exhibited lower levels of baseline prolactin and PRL/volume ratios.

The diagnosis between a prolactinoma and a non-functioning pituitary adenoma can be difficult, particularly when the size of the tumor in question is small. The most recent consensus statement put forth by the Pituitary Society in 2023 suggested that prolactin levels above 200 ng/ml in the setting of a sellar mass are strongly suggestive of a prolactinoma [9]. However, for levels below 200 ng/ml, size-adapted cut-offs for prolactin levels have been studied to differentiate between prolactinomas versus other pituitary tumors. In a prior study from our institution, we compared prolactin levels and pre-operative tumor volume from surgically resected, histopathologically confirmed prolactinomas versus non-functioning pituitary adenomas. There was a strong correlation between prolactinoma size and serum prolactin level with cut-offs of 43.65 ng/ml for tumors under 0.5 cm^3, 60.05 ng/ml for those between 0.5 and 4 cm^3, and 248.15 ng/ml for those > 4 cm^3 [6]. Others have proposed a diagnostic prolactin cut-off value of 55.65 ng/ml [10], 94 ng/ml [11], even some as low as 38.6 ng/ml [12]. The mean prolactin level in our current study of 59.4 ng/ml is comparable to these previous studies. Unlike our previous study [6], we did not find a significant correlation between prolactin levels and tumor volume. That said, our cohort was limited to microadenomas, defined by measuring up to 1 cm in greatest diameter, with a mean volume of 95.9 mm^3, well below the tumor volumes studied in our previous study. In addition, when we compared patients with tumor volumes above and below this mean volume, we did find a significant difference in baseline prolactin levels. With a greater sample size, we suspect there might be an underlying correlation between prolactin levels and tumor volume, even when limited to microadenomas.

In addition to prolactin level cut-offs for various tumor volume thresholds, we explored the utility of a PRL/volume ratio in predicting clinical outcomes. Within our microadenoma cohort, we found that among patients who were initially surveilled, those who would go on to need surgery had significantly greater baseline PRL/volume ratios than in those who were successfully monitored with serial imaging. That said, our sample size for surgically treated patients was extremely small and therefore, our findings should be interpreted with caution. On the other hand, the PRL/volume ratio did not predict patterns of failure with medical management, likely reflecting the fact that the biology of tumor resistance to dopaminergic therapy is not dependent upon baseline prolactin levels. Other studies in the literature have also explored the role of PRL/volume ratios in diagnosing prolactinomas from other pituitary tumors with mild to moderately elevated prolactin levels albeit in tumor of much larger size and measured in cm^3 rather than mm^3 in our study. Cho et al. performed a prolactin to volume ratio analysis and found that tumors with a PRL/volume ratio > 100 ng/ml/cm^3 were predictive of distinguishing prolactinomas from other pituitary tumors [13]. Likewise, Huang et al. reported a PRL/volume ratio of 54 ng/ml/cm^3 to have the highest diagnostic value in patients with pituitary adenomas and elevated prolactin levels but still under 250 ng/ml [10]. Faje et al. reported that a cutoff of 65 ng/ml/cm^3 could discriminate between prolactinomas versus nonfunctioning pituitary adenomas with elevated prolactin levels due to stalk effect [14].

There are no clear guidelines on treatment of suspected microprolactinomas. The proposed treatment algorithm put forth most recently by the Pituitary Society recommends initiating treatment based on factors such as male sex, the desire to conceive, young age, a history of a psychiatric disorder, among others. Surveillance may be considered for postmenopausal women and/or eugonadal premenopausal women not interested in conceiving [9]. Additionally, there can be mild but undesirable side effects with dopamine

agonist therapy that can significantly impair quality of life with long-term usage, including gastric issues, nausea, dizziness, and fatigue [15, 16]. Likewise, there can be mood changes and impulsivity that make patients with existing psychiatric disorders a relative contraindication to use of dopamine agonists [17]. In our study, we found that essentially all patients who were surveilled, aside from one, demonstrated either stability of their lesion size and/or spontaneous shrinkage on further surveillance imaging. In addition, these patients presented either asymptomatically as incidental radiographic findings or with symptoms, most commonly mild menstrual irregularities that were not significantly impairing their quality of life.

The decision to surgically resect prolactinomas upfront remains controversial, particularly for microadenomas that are not causing visual deficits, and is largely due to patient preference [18, 19]. In our cohort, half of the surgically treated patients had failed prior medical therapy while the remaining half preferred surgery after their tumors demonstrated interval growth on repeat imaging. Although we found significantly higher baseline prolactin levels in patients who were surgically treated versus medically treated or observed, our small sample size limits any overarching conclusions on whether any meaningful cut-off exists to recommend surgery upfront over medical therapy for suspected microprolactinomas.

Despite recommendations that certain patients with microprolactinomas may be reasonably observed, there is a lack of data in the literature on the natural history of observed prolactinomas [4]. Schlechte et al. performed a prospective study of 30 women with hyperprolactinemia, 13 of whom had serial radiographic studies and initial findings suggestive of a pituitary adenoma [5]. Four of these patients had tumor shrinkage, 7 remained stable, and 2 had tumor progression. Feldkamp et al. likewise conducted a prospective study of 67 patients with incidental findings of a pituitary adenoma, 42 of whom had microadenomas and 8 of whom had prolactinomas. Only 3.2% of patients with microadenomas demonstrated tumor growth over a mean follow-up period of 2.7 years [20]. Compared to the existing literature, our study is to our knowledge the largest thus far to report the natural history of microprolactinomas. Notably, we found that among the 26 patients that were surveilled, only 1 patient's tumor grew over the follow-up period, while half of these patients demonstrated spontaneous tumor shrinkage at a statistically significant rate of 3.67 mm^3/year. While we did not find significant differences in baseline prolactin levels or volumes in tumors that shrunk versus remained stable, we did find significant variations in baseline prolactin levels and PRL/volume ratios in patients who were successfully surveilled versus requiring intervention. Currently, the literature on microprolactinomas has been focused on diagnostically differentiating these tumors from other pituitary adenomas. Additional studies correlating these tumors with clinical outcomes are needed to ascertain whether certain prolactin and volume relationship cut-offs can be made to identify patients for whom these tumors can be surveilled without any initial intervention.

A limitation of our study is that the majority of our patient cohort did not have histopathologic diagnosis of a prolactinoma, given very few patients underwent surgical resection. Furthermore, among the limited number of patients who had surgery, less than half had histopathologically confirmed diagnosis of a prolactinoma with no correlation with baseline prolactin levels or PRL/volume ratios. As such, it is entirely possible that a subset of our patients, particularly those with very low prolactin levels, may have been harboring non-functioning pituitary adenomas with elevated prolactin levels due to stalk effect, resulting in mild hyperprolactinemia. That said, stalk effect is rare in pituitary microadenomas due to their inherent small size [11]. In addition, there are other etiologies of elevated prolactin levels, such as kidney or liver disease, a myriad of drugs, and even normal physiological responses to pregnancy, lactation, exercise, and sleep [4]. While most of our patients routinely undergo evaluation by a neuro-endocrinologist, this retrospective study did not control for excluding patients who were felt to have elevated prolactin levels due to another cause. That said, even if our sample size may have been diluted by the undetected presence of true non-functioning pituitary adenomas, our data suggest that small pituitary adenomas with mildly elevated prolactin levels may be reasonably observed, regardless of their true underlying histology. While the lack of definitive diagnosis of a prolactinoma is a major limitation of our manuscript, our patient cohort also reflects a common clinical scenario where the natural history and management of a patient with a suspected microadenoma with mildly elevated prolactin levels remains heterogeneous and unclear. As such, our findings provide further insight into how these patients can be managed moving forwards, based on their size and relative prolactin level at time of diagnosis.

In this multicenter retrospective study, we reported observations from the largest known cohort of suspected microprolactinomas to date. We found that within this subset of microadenomas of prolactinoma origin, tumors that exhibit over 95.9 mm^3 demonstrate more convincingly elevated prolactin levels. Likewise, tumors with baseline prolactin levels over 50 ng/ml were more inclined to undergo medical treatment. Of note, through volumetric analysis of tumors that were surveilled over the long-term, we found that tumors with prolactin levels below 50 ng/ml tended to spontaneously shrink over time. Likewise, we found that in tumors that were surveilled, an elevated baseline PRL/

volume ratio of > 8 ng/ml/mm^3 may be indicative of potential tumor growth that may necessitate medical and/or surgical intervention. Further studies focused particularly on the management of small pituitary adenomas with elevated prolactin, suggestive of a microprolactinoma, are needed to better define prolactin and volumetric cut-offs that may guide the decision to observe these tumors versus intervene.

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Author contributions C.S.H. wrote the main manuscript. C.S.H., J.C., C.O. prepared the figures. All authors contributed to clinical data acquisition and analysis. All authors reviewed the manuscript. Senior oversight of the manuscript was provided by C.E.C., L.M., T.R.S.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

Ethics approval This was a retrospective study conducted under an IRB-approved protocol (#2015P002352) at Brigham and Women's Hospital in Boston, MA, USA. Due to the retrospective nature of the study, the requirement for informed consent was waived.

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