Management of Incidentally Found Nonfunctional Pituitary Tumors

Mark E. Molitch, MD

KEYWORDS

• Adenoma • Pituitary • Incidentaloma • Tumor • Transsphenoidal surgery

KEY POINTS

- Patients with pituitary incidentalomas should be evaluated for tumor hypersecretion.
- Those with macroadenomas should be evaluated for hypopituitarism, visual-field defects, and other mass effects.
- Visual-field defects, tumor growth, and hypopituitarism are indications for surgery.
- Deficiencies in corticotropin/cortisol and thyrotropin/thyroxine should be corrected before any surgery.
- Tumor growth in patients who do not undergo surgery can be expected in 10.6% of microadenomas and 24.1% of macroadenomas.
- For patients without specific indications for surgery, surveillance magnetic resonance imaging may need to be performed for up to 20 years.

INTRODUCTION

Clinically nonfunctioning adenomas (CNFA) of the pituitary, by definition, produce no clinical syndrome related to overproduction of tumor hormones. Studies have shown, however, that 70% to 80% of CNFAs produce gonadotropins or their subunits, and thus are actually gonadotroph adenomas.[1] A few per cent also stain for corticotropin, growth hormone (GH), prolactin (PRL), or thyrotropin; because these hormones are not secreted in sufficient quantities to cause clinical syndromes, such tumors are referred to as "silent" corticotroph, somatotroph, lactotroph, or thyrotroph adenomas.[2]

Although large CNFAs often present because they cause significant hypothalamic/pituitary dysfunction or visual symptoms, others may be completely asymptomatic, being detected either at autopsy or as incidental findings on magnetic resonance imaging (MRI) or computed tomography (CT) scans performed for other reasons. These asymptomatic adenomas are referred to as pituitary incidentalomas. Several other lesions also may be found in the sellar area and may mimic a pituitary adenoma, including craniopharyngiomas, Rathke cleft cysts, meningiomas, gliomas, dysgerminomas, cysts, hamartomas, metastases, and focal areas of infarction.[3–6] Lymphocytic infiltration of the pituitary can also masquerade as a pituitary adenoma.[7]

Statistically, some normal individuals must have pituitaries that exceed the normal size boundary of 9 mm (+3 standard deviations in healthy subjects[8–10]). Chanson and colleagues[11] reported several patients with "normal pituitary hypertrophy"; on MRI, these pituitaries had homogeneous isointense signals, enhanced homogeneously with

Disclosure: The author has served as a Consultant for Abbott Laboratories and receives research support from Eli Lilly & Co. and Novo-Nordisk, companies which make various hormone replacement therapies used for hypopituitarism.
Division of Endocrinology, Metabolism and Molecular Medicine, Northwestern University Feinberg School of Medicine, 645 North Michigan Avenue, Suite 530, Chicago, IL 60611, USA
E-mail address: molitch@northwestern.edu

Neurosurg Clin N Am 23 (2012) 543–553
http://dx.doi.org/10.1016/j.nec.2012.06.003
1042-3680/12/$ – see front matter

contrast, and in 2 cases had normal pituitary tissue found at surgery.

This article reviews the epidemiology and management of patients with pituitary mass lesions incidentally found on head MRI or CT done for some reason other than suspected pituitary disease; that is, pituitary incidentalomas.

PREVALENCE OF PITUITARY INCIDENTALOMAS

Autopsy Findings

Pituitary adenomas have been found at autopsy in 1.5% to 31% of subjects not suspected of having pituitary disease while alive (**Table 1**).[3,12–43] The average frequency of finding an adenoma for these studies, which examined a total of 19,387 pituitaries, is 10.7%. The tumors are distributed equally throughout the age groups (range 16–86 years) and between the sexes. In the studies in which PRL immunohistochemistry was performed, 22% to 66% stained positively for PRL.[18,20,21,26,29–31,33–36,38,39] Detailed immunohistochemical analysis of 334 pituitary adenomas found in 316 pituitaries of 3048 autopsy cases in one series showed that 39.5% stained for PRL, 13.8% for corticotropin, 7.2% for gonadotropins or α subunits, 1.8% for GH, 0.6% for thyrotropin, and 3.0% for multiple hormones.[39]

In these postmortem studies all but 7 of the tumors were less than 10 mm in diameter. The relative lack of macroadenomas in these autopsy studies suggests that growth from a microadenoma to a macroadenoma must be an exceedingly uncommon event, and/or that virtually all macroadenomas come to clinical attention and, therefore, are not included in autopsy findings. There is a separate report of an additional 3 macroadenomas being found at autopsy.[44]

CT and MRI Scans in Normal Individuals

Three series have evaluated CT scans of the sella in normal subjects who were having such scans for reasons unrelated to possible pituitary disease, finding discrete areas of low density greater than 3 mm in diameter in 4% to 20%.[3,45,46] Two similar studies have been performed using MRI. Chong and colleagues[47] found focal pituitary gland hypodensities of 2 to 5 mm in 20 of 52 normal subjects with nonenhanced images using a 1.5-T scanner and 3-mm thick sections. With similar scans but with gadolinium-DTPA (diethylenetriamine pentaacetic acid) enhancement, Hall and colleagues[48] found focal areas of decreased intensity 3 mm or greater in diameter in 34%, 10%, and 2% of 100 volunteers, depending on whether there was agreement on the diagnosis between 1, 2, or 3 independent reviewing neuroradiologists.

Sellar lesions greater than 10 mm in diameter have not been found in these small studies of consecutive normal individuals, similar to the very limited number found at autopsy. However, Nammour and colleagues[49] found that of 3550 consecutive CT scans done in men with a mean age of 57 years for the symptoms of change in mental status, headache, or possible metastases, 7 (0.2%) were found to have pituitary macroadenomas ranging from 1.0 to 2.5 cm in size; all were thought to be CNFAs after hormonal evaluation. Similarly, when nonenhanced MRI scans were performed without specific views of the sellar area in asymptomatic normal subjects, macroadenomas were found in 0.16% of 3672 subjects in a study by Yue and colleagues[50] and in 0.3% of 2000 subjects in a study by Vernooij and colleagues.[51] Furthermore, macroadenomas have been reported as incidental findings.[52]

Clinical Experience with Pituitary Incidentalomas

Clinically, patients with incidental macroadenomas are commonly seen in everyday practice. In 10 series totaling 513 patients reported with pituitary CNFAs who were not treated either surgically or medically, thereby giving an indication of their natural history, 353 (68.8%) had macroadenomas and 260 (31.2%) had microadenomas (**Table 2**).[53–62] However, these were not all true incidentalomas. Many had tumors 2 cm or more in diameter and many were symptomatic with hypopituitarism or visual-field defects, but for a variety of reasons surgery was not performed. For example, in the series reported by Karavitaki and colleagues,[61] only one-half of the 24 macroadenomas were incidental findings and 11 had varying degrees of hypopituitarism. In this series, 5 of the patients had major visual-field defects but did not have surgery either because of major comorbidities (3 patients) or because the patient did not wish surgery (2 patients).[61] Similarly, in the series of 28 patients with macroadenomas reported by Dekkers and colleagues,[62] only 6 (21%) were truly incidentalomas, with 44% having hypopituitarism and 46% having visual-field defects. Nevertheless, the proportion of patients with macroadenomas found clinically as incidentalomas is much greater than would be expected based on the autopsy or radiology findings. These data suggest that the mass effects of such tumors may have caused some of the symptomatology causing the patients to have the scans in the first place, even in those in whom there were no true visual-field defects or hypopituitarism.

Table 1
Frequency of pituitary adenomas found at autopsy

Authors,[Ref.] Year	No. of Pituitaries Examined	No. of Adenomas Found	Frequency (%)	No. of Macroadenomas Found	Stain Positive for Prolactin (%)
Susman,[12] 1933	260	23	8.8	—	—
Close,[13] 1934	250	23	9.2	—	—
Costello,[14] 1936	1000	225	22.5	0	—
Sommers,[15] 1959	400	26	6.5	0	—
McCormick and Halmi,[16] 1971	1600	140	8.8	0	—
Haugen,[17] 1973	170	33	19.4	—	—
Kovacs et al,[18] 1980	152	20	13.2	2	53
Landolt,[19] 1980	100	13	13.0	0	—
Mosca et al,[20] 1980	100	24	24.0	0	23
Burrows et al,[21] 1981	120	32	26.7	0	41
Parent et al,[22] 1981	500	42	8.4	1	—
Muhr et al,[23] 1981	205	3	1.5	0	—
Max et al,[24] 1981	500	9	1.8	—	—
Schwezinger and Warzok,[25] 1982	5100	485	9.5	0	—
Chambers et al,[3] 1982	100	14	14.0	0	—
Coulon et al,[26] 1983	100	10	10.0	0	60
Siqueira and Guembarovski,[27] 1984	450	39	8.7	0	—
Char and Persaud,[28] 1986	350	35	10.0	0	—
Gorczyca and Hardy,[29] 1988	100	27	27.0	0	30
El-Hamid et al,[30] 1988	486	97	20.0	0	48
Scheithauer et al,[31] 1989	251	41	16.3	0	66
Kontogeorgos et al,[32] 1991	470	49	10.4	0	—
Marin et al,[33] 1992	210	35	16.7	0	32
Sano et al,[34] 1993	166	15	9.0	0	47
Teramoto et al,[35] 1994	1000	51	5.1	0	30
Camaris et al,[36] 1995	423	14	3.2	0	44
Tomita and Gates,[37] 1999	100	24	24.0	—	—
Kurosaki et al,[38] 2001	692	79	11.4	1	24
Buurman and Saeger,[39] 2006	3048	334	11.0	3	40
Rittierodt and Hori,[40] 2007	228	7	3.0	0	—
Furgal-Borzych et al,[41] 2007	151	47	31.1	0	21
Kim et al,[42] 2007	120	7	6.7	0	29
Adhakhani et al,[43] 2011	485	61	—	—	—
Total	19,387	2084	10.7%	7	—

The final column shows the percentage of tumors that had positive immunostaining for prolactin, indicating that they were lactotroph adenomas.

Table 2
Changes in size of pituitary incidentalomas

	Microadenomas				Macroadenomas				
Authors,[Ref.] Year	Total	Increased	Decreased	No Change	Total	Enlarged	Decreased	No Change	Years Followed
Donovan and Corenblum,[53] 1995	15	0	0	15	16	4[a]	0	12	6–7
Reincke et al,[54] 1990	7	1	1	5	7	2	0	5	8
Nishizawa et al,[55] 1998	—	—	—	—	28	2[a]	0	26	5.6
Feldkamp et al,[56] 1999	31	1	1	29	19	5	1	13	2.7
Igarashi et al,[57] 1999	1	0	0	1	22	6	10	6	5.1
Sanno et al,[58] 2003	74	10	7	57	165	20[a]	22	123	2.3
Fainstein Day et al,[59] 2004	11	1	0	10	7	1	0	6	3.2
Arita et al,[60] 2006	5	2	0	3	37	19[a]	0	18	5.2
Karavitaki et al,[61] 2007	16	2	1	13	24	12	4	8	3.6
Dekkers et al,[62] 2007	—	—	—	—	28	14	8	6	7.1
Total	160	17 (10.6%)	10 (6.3%)	133 (83.1%)	353	85 (24.1%)	45 (12.7%)	223 (63.2%)	—

[a] A total of 7 cases in these series had tumor enlargement caused by apoplexy.

EVALUATION OF PATIENTS WITH PITUITARY INCIDENTALOMAS

Endocrinologic Evaluation for Pituitary Hyperfunction

As the most common lesion in the sella is a pituitary adenoma, it is reasonable to evaluate patients for hormone oversecretion, regardless of the size of the lesion.[63,64] Many of the changes occurring with hormone oversecretion syndromes may be quite subtle and only slowly progressive; therefore, screening for hormonal oversecretion is warranted even in patients with no clinical evidence of hormone oversecretion. "Silent" somatotroph and corticotroph adenomas have been reported many times, but it is not clear whether such patients with minimal clinical evidence of hormone oversecretion are free from the increased risk for the more subtle cardiovascular, bone, oncologic, and possibly other adverse effects usually associated with such tumors. Indeed, there is emerging evidence that subclinical Cushing syndrome caused by adrenal incidentalomas is associated with significantly increased prevalence of diabetes, hypertension, obesity, osteoporosis, and cardiovascular risk.[65] Whether there is a similar increased risk for these comorbidities with silent corticotroph adenomas is unknown. Furthermore, some investigators have reported that silent corticotroph adenomas have a worse prognosis than those with overt disease with respect to aggressiveness following initial surgery,[66,67] but this has not been found in other series.[62,68,69] Progression to overt Cushing disease over time was reported in 4 of 22 (18%) of cases in one series.[70] It is not clear how many of these patients have nonsuppressible serum cortisol levels or elevated urinary free cortisol levels, but Lopez and colleagues[71] found suppressed corticotropin secretion and hypocortisolism in 2 of 12 patients following resection of silent corticotropin-secreting adenomas.

Screening for hormone oversecretion in such patients has been questioned as to its cost-effectiveness.[72–74] However, evidence from the series of Fainstein Day and colleagues[59] suggests such screening is worthwhile, as 7 of their 46 patients turned out to have prolactinomas, and of the 13 who ended up going to surgery and having immunohistochemistry performed, 2 adenomas (15%) were GH positive and 4 (31%) were plurihormonal adenomas.

A serum PRL should be obtained, but it is very important to distinguish between PRL production by a tumor versus hyperprolactinemia from stalk dysfunction caused by a macroadenoma.[75] PRL levels are usually higher than 200 ng/mL for hormone-secreting macroadenomas, and lower numbers suggest stalk dysfunction.[76–78] For very large tumors, the sample should be diluted 1:100 to avoid the "hook effect,"[79,80] in which very high PRL levels may saturate the antibodies in 2-site assays; however, this is not necessary in all assays. An insulin-like growth factor 1 (IGF-1) test is probably sufficient to screen for acromegaly but if this cannot be performed, it may be necessary to demonstrate nonsuppression of GH levels by hyperglycemia during an oral glucose tolerance test.[81]

The best screening tests for Cushing syndrome have traditionally been the overnight dexamethasone suppression test and the 24-hour urinary free cortisol, and more recently, the assessment of a midnight salivary cortisol.[82,83] An abnormal midnight salivary cortisol has been found to have greater than 93% specificity and sensitivity for diagnosing Cushing syndrome.[84] Because the patients may have little in the way of symptoms, it is likely that the 24-hour urine free cortisol will be normal and an overnight 1-mg dexamethasone suppression test or a midnight salivary cortisol might be better tests to diagnose early Cushing disease. Because of the high variability of corticotropin levels, even in patients with overt Cushing disease, corticotropin levels are probably not worth measuring. However, some participants on The Endocrine Society Taskforce that wrote the Pituitary Incidentaloma Clinical Practice Guideline of the Society thought that measurement of corticotropin levels might be useful.[64] Any abnormality found on such screening would then need to be pursued with more definitive testing. Despite the fact that most CNFAs are gonadotroph adenomas, gonadotropin oversecretion rarely causes clinical symptoms, and such a finding would not influence therapy; therefore, there is no reason to screen for this.

Endocrinologic Evaluation for Hypopituitarism

Microadenomas have generally not been thought to cause disruption of normal pituitary function. Of the 22 patients with suspected microadenomas evaluated in the series of Reincke and colleagues[54] and Donovan and Corenblum,[53] all had normal pituitary function. However, Yuen and colleagues[85] found deficiencies of one or more pituitary hormones in 50% of 38 patients with clinically nonfunctioning microadenomas. Larger lesions are much more likely to cause varying degrees of hypopituitarism, and up to 41% of patients with macroadenomas have been found to have hypopituitarism.[50,52,56,57] Thus, all patients with macroadenomas should be screened

for hypopituitarism, but whether all patients with microadenomas should be similarly screened is controversial.

Screening for deficiencies of thyrotropin, corticotropin, GH, and gonadotropins consists of assessing symptoms of possible hypopituitarism in the patient and measurement of levels of free thyroxine (thyrotropin is not sensitive for diagnosing central hypothyroidism), 8 AM cortisol, IGF-1, and testosterone or estradiol. If the 8 AM cortisol level is less than 18 μg/dL, additional measures may be necessary to diagnose a deficiency of corticotropin/cortisol.[86,87] In postmenopausal women, the finding of low gonadotropins would indicate hypopituitarism.[64] Deficiencies of thyroxine and cortisol should always be replaced when diagnosed regardless of whether surgery is to be done. Gonadal hormone and GH replacements are initiated as clinically indicated, but not necessarily before surgery and generally after more detailed testing, including GH stimulation tests.[86,87] It should be remembered that those found to be corticotropin/cortisol deficient need stress doses of steroids during surgery. Because surgery can both improve and worsen pituitary function, retesting and reassessment several weeks after any surgery is mandatory. In patients who are not hypopituitary or who have partial hypopituitarism and who do not undergo surgery, an increase in tumor size on surveillance MRI is an indication for repeat assessment for hypopituitarism. Whether repeat testing is indicated in such patients in the absence of evidence for tumor growth is controversial.[64]

NATURAL HISTORY AND FOLLOW-UP OF INCIDENTAL CNFAs

In the 10 series mentioned that reported on the follow-up of patients with pituitary CNFAs that were not treated, most were incidentalomas; however, in many cases the adenomas were symptomatic but not treated for a variety of reasons (see **Table 2**). Of the 160 patients with microadenomas reported in these series, 17 (10.6%) experienced tumor growth, 10 (6.3%) showed evidence of a decrease in tumor size, and 133 (83.1)% remained unchanged in size in follow-up MRI scans over periods of up to 8 years.[53,54,56–61] Of the 353 patients with macroadenomas, 85 (24.1%) showed evidence of tumor enlargement, 45 (12.7%) showed evidence of a decrease in tumor size, and 223 (63.2%) remained unchanged in size on follow-up MRI over periods of 8 years.[53–62] In their review of the data from these series, Fernández-Balsells and colleagues[88] expressed the incidence of tumor enlargement per 100 patient-years as 12.53 for macroadenomas and 3.32 for microadenomas. The duration of follow-up of these patients was variable and in their analysis, Dekkers and colleagues[62] suggested that with longer follow-up up to 50% of patients with macroadenomas will have an increase in tumor size. It should be mentioned that of the 59 macroadenomas with an increase in tumor size, in 7 this was due to a hemorrhage into the tumor (see **Table 2**).

The incidence of pituitary apoplexy per 100 patient-years was 1.1 for macroadenomas and 0.4 for microadenomas.[88]

MANAGEMENT OF INCIDENTAL CNFAs

Tumors found to be hypersecreting may be handled in the usual way, generally with dopamine agonists for prolactinomas and surgery for GH and corticotropin-producing tumors. Treatment guidelines for the management of such tumors are readily available.[89–91] For tumors not oversecreting these hormones, the indications for surgery are based initially on mass effects of the tumors and subsequently on tumor-size enlargement.

Microadenomas

For patients with microadenomas, significant tumor enlargement will occur in only 10.6% of patients. Therefore, surgical resection is generally not indicated, and repeated annual scanning for 3 years is indicated to detect tumor enlargement; subsequently, repeat scanning can be done less frequently (**Fig. 1**). Surgery would then be done only for significant tumor enlargement. However, the rate of growth is generally quite slow so that the decision and timing of any surgery would depend on the rate and amount of growth as well as any clinical consequences, such as the development of visual-field defects.

Macroadenomas

Tumors greater than 1 cm in diameter have already indicated a propensity for growth. A careful evaluation of the mass effects of these tumors is indicated, including evaluation of pituitary function and visual field examination if the tumor abuts the chiasm. If there are visual-field defects, surgery is certainly indicated.[64] Because hypopituitarism is potentially correctable with tumor resection, this is also a relative indication for surgery.[92] In the author's opinion, tumors larger than 2 cm should also be considered for surgery simply because of their already demonstrated propensity for growth. Similarly, if a tumor is found to be abutting the optic chiasm, even though testing shows

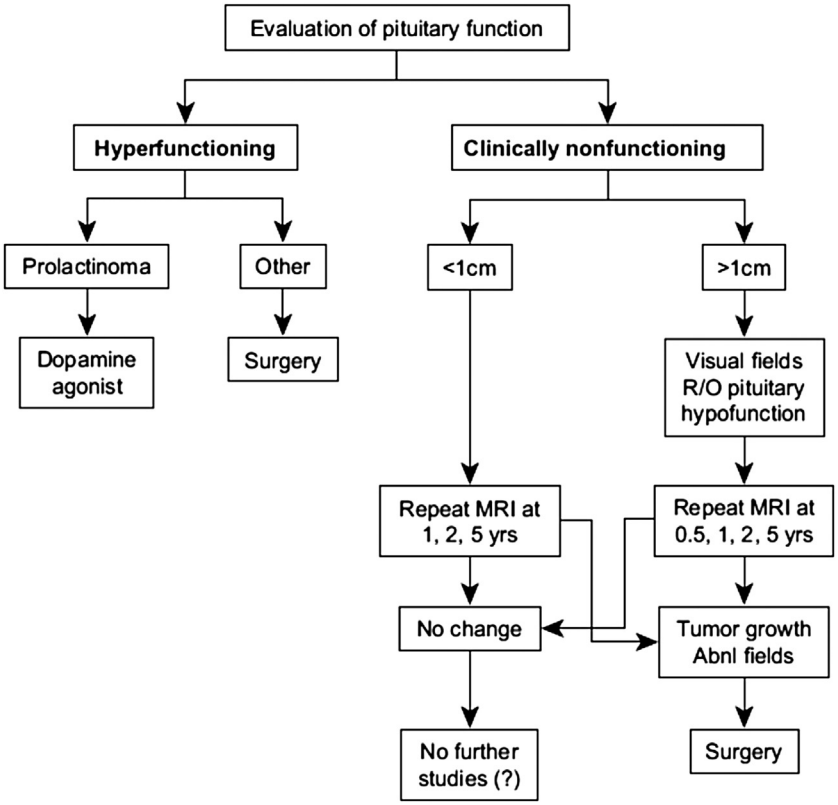

Fig. 1. Flow diagram indicating the approach to the patient found to have a pituitary incidentaloma. The first step is to evaluate patients for pituitary hyperfunction and then treat those found to be hyperfunctioning. Of patients with tumors that are clinically nonfunctioning, those with macroadenomas are evaluated further for evidence of chiasmal compression and hypopituitarism. Scans are then repeated at progressively longer intervals to assess for enlargement of the tumors. Abnl, abnormal; R/O, rule out. (*Reproduced from* Molitch ME. Nonfunctioning pituitary tumors and pituitary incidentalomas. Endocrinol Metab Clin North Am 2008;37:151–71; with permission.)

normal visual fields, consideration should be given to surgery. If surgery is not done, visual fields should be tested at 6- to 12-monthly intervals thereafter.

If a completely asymptomatic lesion is thought to be a pituitary macroadenoma based on radiologic and clinical findings, then a decision could be made to simply repeat scans on a yearly basis, surgery being deferred until there is evidence of tumor growth. Some clinicians would obtain the initial follow-up scan at 6 months to detect potential rapid growers.[64] As indicated earlier, significant tumor growth can be expected in approximately one-quarter of patients with macroadenomas. Hemorrhage into such tumors is uncommon, but anticoagulation may predispose to this complication; surgery would prevent such a complication. When there is no evidence of visual-field defects or hypopituitarism and the patient is asymptomatic, an attempt at medical therapy with a dopamine agonist or octreotide is reasonable, realizing that only about 10% to 20% of such patients will respond with a decrease in tumor size.[93,94] Surgery may be indicated if surveillance scans show evidence of tumor enlargement. As with microadenomas, the decision to proceed with surgery is affected by the rate and extent of growth and any clinical consequences, such as compression of the optic chiasm or the development of pituitary hormone deficiencies, as well as the patient's comorbidities and risks for surgery (see **Fig. 1**).

Attempts have been made to look at the growth rates of those tumors that do grow. Dekkers and colleagues[62] estimated a growth rate of 0.6 mm per year or 236 mm^3 per year. Of their 14 patients who experienced tumor growth, 2 showed evidence of growth by 2 years, 3 more by 3 years, and then 1 each at 4, 5, 6, 7, 12, 15, 17, 20, and 22 years. By contrast, Karavitaki and colleagues[61] found that all but 4 of their 12 patients who experienced macroadenoma regrowth did so by

5 years, although patients also had evidence of tumor growth at 6 and 8 years. Honegger and colleagues[95] found tumor volume doubling times ranging from 0.8 to 27.2 years, emphasizing the tremendous variability of increases in tumor size; there was no correlation between initial tumor size and the rate of tumor-volume doubling. These data suggest that at least for patients with macroadenomas, surveillance MRI scans should be performed for at least 22 years, although the frequency of scanning can certainly be reduced after the first few years if there is no evidence of tumor growth.

SUMMARY

Pituitary incidentalomas are frequently seen in endocrine practice. Although most incidentalomas are either gonadotroph adenomas or truly nonfunctioning, some may be silent lactotroph, somatotroph, or corticotroph adenomas. For CNFAs, hypopituitarism, visual-field defects, and evidence of tumor growth are indications for surgery. Growth of nonfunctioning incidentalomas can be expected in 10.6% of microadenomas and 24% of macroadenomas. Periodic surveillance by MRI may be needed for more than 20 years to detect tumor growth.

REFERENCES

1. Young WF, Scheithauer BW, Kovacs KT, et al. Gonadotroph adenoma of the pituitary gland: a clinicopathologic analysis of 100 cases. Mayo Clin Proc 1996;71:649–56.
2. Yamada S, Kovacs K, Horvath E, et al. Morphological study of clinically nonsecreting pituitary adenomas in patients under 40 years of age. J Neurosurg 1991;75:902–5.
3. Chambers EF, Turski PA, LaMasters D, et al. Regions of low density in the contrast-enhanced pituitary gland: normal and pathologic processes. Radiology 1982;144:109–13.
4. Elster AD. Modern imaging of the pituitary. Radiology 1993;187:1–14.
5. Freda PU, Wardlaw SL, Post KD. Unusual causes of sellar/parasellar masses in a large transsphenoidal surgical series. J Clin Endocrinol Metab 1996;81: 3455–9.
6. Naidich MJ, Russell EJ. Current approaches to imaging of the sellar region and pituitary. Endocrinol Metab Clin North Am 1999;28:45–79.
7. Molitch ME, Gilliam MP. Lymphocytic hypophysitis. Horm Res 2007;68(Suppl 5):145–50.
8. Doraiswamy PM, Potts JM, Axelson DA, et al. MR assessment of pituitary gland morphology in healthy volunteers: age- and gender-related differences. AJNR Am J Neuroradiol 1992;13:1295–9.
9. Elster AD, Chen MY, Williams DW, et al. Pituitary gland: MR imaging of physiologic hypertrophy in adolescence. Radiology 1999;174:681–5.
10. Tsunoda A, Okuda O, Sato K. MR height of the pituitary gland as a function of age and sex: especially physiological hypertrophy in adolescence and in climacterium. AJNR Am J Neuroradiol 1997;18:551–4.
11. Chanson P, Daujat F, Young J, et al. Normal pituitary hypertrophy as a frequent cause of pituitary incidentalomas: a follow-up study. J Clin Endocrinol Metab 2001;86:3009–15.
12. Susman W. Pituitary adenoma. Br Med J 1933;2: 1215.
13. Close HG. The incidence of adenoma of the pituitary body in some types of new growth. Lancet 1934;1: 732–4.
14. Costello RT. Subclinical adenoma of the pituitary gland. Am J Pathol 1936;12:205–15.
15. Sommers SC. Pituitary cell relations to body states. Lab Invest 1959;8:588–621.
16. McCormick WF, Halmi NS. Absence of chromophobe adenomas from a large series of pituitary tumors. Arch Pathol 1971;92:231–8.
17. Haugen OA. Pituitary adenomas and the histology of the prostate in elderly men. Acta Pathol Microbiol Scand A 1973;81:425–34.
18. Kovacs K, Ryan N, Horvath E. Pituitary adenomas in old age. J Gerontol 1980;35:16–22.
19. Landolt AM. Biology of pituitary microadenomas. In: Faglia G, Giovanelli MA, MacLeod RM, editors. Pituitary microadenomas. New York: Academic Press; 1980. p. 107–22.
20. Mosca L, Solcia E, Capella C, et al. Pituitary adenomas: surgical versus post-mortem findings today. In: Faglia G, Giovanelli MA, MacLeod RM, editors. Pituitary microadenomas. New York: Academic Press; 1980. p. 137–42.
21. Burrows GN, Wortzman G, Rewcastle NB, et al. Microadenomas of the pituitary and abnormal sellar tomograms in an unselected autopsy series. N Engl J Med 1981;304:156–8.
22. Parent AD, Bebin J, Smith RR. Incidental pituitary adenomas. J Neurosurg 1981;54:228–31.
23. Muhr C, Bergstrom K, Grimelius L, et al. A parallel study of the roentgen anatomy of the sella turcica and the histopathology of the pituitary gland in 205 autopsy specimens. Neuroradiology 1981;21:55–65.
24. Max MB, Deck MD, Rottenberg DA. Pituitary metastasis: incidence in cancer patients and clinical differentiation from pituitary adenoma. Neurology 1981; 31:998–1002.
25. Schwezinger G, Warzok R. Hyperplasien und adenome der hypophyse im unselektierten sektionsgut. Zentralbl Allg Pathol 1982;126:495–8 [in German].

26. Coulon G, Fellmann D, Arbez-Gindre F, et al. Les adenome hypophysaires latents. Etude autopsique. Sem Hop 1983;59:2747–50 [in French].
27. Siqueira MG, Guembarovski AL. Subclinical pituitary microadenomas. Surg Neurol 1984;22:134–40.
28. Char G, Persaud V. Asymptomatic microadenomas of the pituitary gland in an unselected autopsy series. West Indian Med J 1986;35:275–9.
29. Gorczyca W, Hardy J. Microadenomas of the human pituitary and their vascularization. Neurosurgery 1988;22:1–6.
30. El-Hamid MW, Joplin GF, Lewis PD. Incidentally found small pituitary adenomas may have no effect on fertility. Acta Endocrinol 1988;117:361–4.
31. Scheithauer BW, Kovacs KT, Randall RV, et al. Effects of estrogen on the human pituitary: a clinicopathologic study. Mayo Clin Proc 1989;64:1077–84.
32. Kontogeorgos G, Kovacs K, Horvath E, et al. Multiple adenomas of the human pituitary. A retrospective autopsy study with clinical implications. J Neurosurg 1991;74:243–7.
33. Marin F, Kovacs KT, Scheithauer BW, et al. The pituitary gland in patients with breast carcinoma: a histologic and immunocytochemical study of 125 cases. Mayo Clin Proc 1992;67:949–56.
34. Sano T, Kovacs KT, Scheithauer BW, et al. Aging and the human pituitary gland. Mayo Clin Proc 1993;68: 971–7.
35. Teramoto A, Hirakawa K, Sanno N, et al. Incidental pituitary lesions in 1,000 unselected autopsy specimens. Radiology 1994;193:161–4.
36. Camaris C, Balleine R, Little D. Microadenomas of the human pituitary. Pathology 1995;27:8–11.
37. Tomita T, Gates E. Pituitary adenomas and granular cell tumors. Incidence, cell type, and location of tumor in 100 pituitary glands at autopsy. Am J Clin Pathol 1999;111:817–25.
38. Kurosaki M, Saeger W, Lüdecke DK. Pituitary tumors in the elderly. Pathol Res Pract 2001;197:493–7.
39. Buurman H, Saeger W. Subclinical adenomas in postmortem pituitaries: classification and correlations to clinical data. Eur J Endocrinol 2006;154: 753–8.
40. Rittierodt M, Hori A. Pre-morbid morphological conditions of the human pituitary. Neuropathology 2007;27:43–8.
41. Furgal-Borzych A, Lis GJ, Litwin JA, et al. Increased incidence of pituitary microadenomas in suicide victims. Neuropsychology 2007;55:163–6.
42. Kim JH, Seo JS, Lee BW, et al. The characteristics of incidental pituitary microadenomas in 120 Korean forensic autopsy cases. J Korean Med Sci 2007; 22(Suppl):S61–5.
43. Adhakhani K, Kadivar M, Kazemi-Esfeh S, et al. Prevalence of pituitary incidentaloma in the Iranian cadavers. Indian J Pathol Microbiol 2011; 54:692–4.
44. Auer RN, Alakija P, Sutherland GR. Asymptomatic large pituitary adenomas discovered at autopsy. Surg Neurol 1996;46:28–31.
45. Wolpert SM, Molitch ME, Goldman JA, et al. Size, shape and appearance of the normal female pituitary gland. AJNR Am J Neuroradiol 1984;5:263–7.
46. Peyster RG, Adler LP, Viscarello RR, et al. CT of the normal pituitary gland. Neuroradiology 1986;28: 161–5.
47. Chong BW, Kucharczyk AW, Singer W, et al. Pituitary gland MR: a comparative study of healthy volunteers and patients with microadenomas. AJNR Am J Neuroradiol 1994;15:675–9.
48. Hall WA, Luciano MG, Doppman JL, et al. Pituitary magnetic resonance imaging in normal human volunteers: occult adenomas in the general population. Ann Intern Med 1994;120:817–20.
49. Nammour GM, Ybarra J, Naheedy MH, et al. Incidental pituitary macroadenoma: a population-based study. Am J Med Sci 1997;314:287–91.
50. Yue NC, Longsteth WT Jr, Elster AD, et al. Clinically serious abnormalities found incidentally at MR imaging of the brain: data from the Cardiovascular Health Study. Radiology 1997;202:41–6.
51. Vernooij MW, Ikram A, Tanghe HL, et al. Incidental findings on brain MRI in the general population. N Engl J Med 2007;357:1821–8.
52. Chacko AG, Chandy MJ. Incidental pituitary macroadenomas. Br J Neurosurg 1992;6:233–6.
53. Donovan LE, Corenblum B. The natural history of the pituitary incidentaloma. Arch Intern Med 1995;153: 181–3.
54. Reincke M, Allolio B, Saeger W, et al. The 'incidentaloma' of the pituitary gland. Is neurosurgery required? JAMA 1990;263:2772–6.
55. Nishizawa S, Ohta S, Yokoyama T, et al. Therapeutic strategy for incidentally found pituitary tumors ("pituitary incidentalomas"). Neurosurgery 1998;43: 1344–8.
56. Feldkamp J, Santen R, Harms E, et al. Incidentally discovered pituitary lesions: high frequency of macroadenomas and hormone-secreting adenomas - results of a prospective study. Clin Endocrinol 1999;51:109–13.
57. Igarashi T, Saeki N, Yamaura A. Long-term magnetic resonance imaging follow-up of asymptomatic sellar tumors. Their natural history and surgical indications. Neurol Med Chir (Tokyo) 1999;39:592–9.
58. Sanno N, Oyama K, Tahara S, et al. A survey of pituitary incidentaloma in Japan. Eur J Endocrinol 2003; 149:123–7.
59. Fainstein Day P, Guitelman M, Artese R, et al. Retrospective multicentric study of pituitary incidentalomas. Pituitary 2004;7:145–8.
60. Arita K, Tominaga A, Sugiyama K, et al. Natural course of incidentally found nonfunctioning pituitary adenoma, with special reference to pituitary

apoplexy during follow-up examination. J Neurosurg 2006;104:884–91.
61. Karavitaki N, Collison K, Halliday J, et al. What is the natural history of nonoperated, nonfunctioning pituitary adenomas? Clin Endocrinol 2007;67: 938–43.
62. Dekkers OM, Hammer S, de Keizer RJ, et al. The natural course of non-functioning pituitary macroadenomas. Eur J Endocrinol 2007;156:217–24.
63. Dekkers OM, Pereira AM, Romijn JA. Treatment and follow-up of clinically nonfunctioning pituitary macroadenomas. J Clin Endocrinol Metab 2008;93: 3717–26.
64. Freda PU, Beckers M, Katznelson L, et al. Pituitary incidentaloma: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2011;96: 894–904.
65. Angeli A, Terzolo M. Adrenal incidentaloma—a modern disease with old complications. J Clin Endocrinol Metab 2002;87:4869–71.
66. Scheithauer BW, Jaap AJ, Horvath E, et al. Clinically silent corticotroph tumors of the pituitary gland. Neurosurgery 2000;47:723–9.
67. Bradley KJ, Wass JA, Turner HE. Non-functioning pituitary adenomas with positive immunoreactivity for ACTH behave more aggressively than ACTH immunonegative tumours but do not recur more frequently. Clin Endocrinol 2003;58:59–64.
68. Soto-Ares G, Cortet-Rudelli C, Assaker R, et al. MRI protocol technique in the optimal therapeutic strategy of nonfunctioning pituitary adenomas. Eur J Endocrinol 2002;146:179–86.
69. Park P, Chandler WF, Barkan AL, et al. The role of radiation therapy after surgical resection of nonfunctional pituitary macroadenomas. Neurosurgery 2004;55:100–6.
70. Baldeweg SE, Pollock JR, Powell M, et al. A spectrum of behaviour in silent corticotroph pituitary adenomas. Br J Neurosurg 2005;19:38–42.
71. Lopez JA, Kleinschmidt-DeMasters BK, Sze CI, et al. Silent corticotroph adenomas: further clinical and pathological observations. Hum Pathol 2004; 35:1137–47.
72. King JT Jr, Justice AC, Aron DC. Management of incidental pituitary microadenomas: a cost-effectiveness analysis. J Clin Endocrinol Metab 1997;82:3625–32.
73. Krikorian A, Aron D. Evaluation and management of pituitary incidentalomas—revisiting an acquaintance. Nat Clin Pract Endocrinol Metab 2006;2:138–45.
74. Chanson P, Young J. Pituitary incidentalomas. Endocrinologist 2003;13:124–35.
75. Casanueva FF, Molitch ME, Schlechte JA, et al. Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. Clin Endocrinol 2006;65:265–73.
76. Molitch ME, Reichlin S. Hypothalamic hyperprolactinemia: neuroendocrine regulation of prolactin secretion in patients with lesions of the hypothalamus and pituitary stalk. In: MacLeod RM, Thorner MO, Scapagnini U, editors. Prolactin. Basic and clinical correlates. Padova (Italy): Liviana Press; 1985. p. 709–19.
77. Arafah MB, Neki KE, Gold RS, et al. Dynamics of prolactin secretion in patients with hypopituitarism and pituitary macroadenomas. J Clin Endocrinol Metab 1995;80:3507–12.
78. Karavitaki N, Thanabalasingham G, Shore HC, et al. Do the limits of serum prolactin in disconnection hyperprolactinaemia need re-definition? A study of 226 patients with histologically verified non-functioning pituitary macroadenoma. Clin Endocrinol 2006;65: 524–9.
79. St-Jean E, Blain F, Comtois R. High prolactin levels may be missed by immunoradiometric assay in patients with macroprolactinomas. Clin Endocrinol 1996;44:305–9.
80. Barkan AL, Chandler WF. Giant pituitary prolactinoma with falsely low serum prolactin: the pitfall of the "high-dose hook effect": case report. Neurosurgery 1998;42:913–5.
81. The Growth Hormone Research Society, The Pituitary Society Consensus Conference. Biochemical assessment and long-term monitoring in patients with acromegaly. J Clin Endocrinol Metab 2004;89:3099–102.
82. Arnaldi G, Angeli A, Atkinson AB, et al. Diagnosis and complications of Cushing's syndrome: a consensus statement. J Clin Endocrinol Metab 2003; 88:5593–602.
83. Findling JW, Raff H. Cushing's syndrome: important issues in diagnosis and management. J Clin Endocrinol Metab 2006;91:3746–53.
84. Carroll T, Raff H, Findling JW. Late-night salivary cortisol measurement in the diagnosis of Cushing's syndrome. Nat Clin Pract Endocrinol Metab 2008;4: 344–50.
85. Yuen KC, Cook DM, Sahasranam P, et al. Prevalence of GH and other anterior pituitary hormone deficiencies in adults with nonsecreting pituitary microadenomas and normal serum IGF-1 levels. Clin Endocrinol 2008;69:292–8.
86. Toogood AA, Stewart PM. Hypopituitarism: clinical features, diagnosis, and management. Endocrinol Metab Clin North Am 2008;37:235–71.
87. Petersenn S, Quabbe HJ, Schöfl C, et al. The rational use of pituitary stimulation tests. Dtsch Arztebl Int 2010;107:437–43.
88. Fernández-Balsells MM, Murad MH, Barwise A, et al. Natural history of nonfunctioning pituitary adenomas and incidentalomas: a systematic review and metaanalysis. J Clin Endocrinol Metab 2011;96:905–12.
89. Melmed S, Casanueva FF, Hoffman AR, et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2011;96:273–88.

90. Melmed S, Colao A, Barkan A, et al. A guideline for acromegaly management: an update. J Clin Endocrinol Metab 2009;94:1509–17.
91. Biller BM, Grossman AB, Stewart PM, et al. Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. J Clin Endocrinol Metab 2008;93:2454–62.
92. Arafah AM. Reversible hypopituitarism in patients with large nonfunctioning pituitary adenomas. J Clin Endocrinol Metab 1986;62:1173–9.
93. Shomali ME, Katznelson L. Medical therapy of gonadotropin-producing and nonfunctioning pituitary adenomas. Pituitary 2002;5:89–98.
94. Colao A, Di Somma C, Pivonello R, et al. Medical therapy for clinically non-functioning pituitary adenomas. Endocr Relat Cancer 2008;15:905–15.
95. Honegger J, Zimmermann S, Psaras T, et al. Growth modeling of non-functioning pituitary adenomas in patients referred for surgery. Eur J Endocrinol 2008; 158:287–94.