Incidentally discovered pituitary masses: pituitary incidentalomas

Dima Abdelmannan and David C Aron†

†Author for correspondence
VA Health Services Research and Development Service Center for Implementation Practice and Research Support, Education Office 14 (W), Louis Stokes
Department of Veterans Affairs Medical Center, 10701 East
Boulevard, Cleveland, OH, USA
Tel.: +1 216 421 3098
Fax: +1 216 231 3427
david.aron@va.gov

With the widespread use of computed tomography and MRI, the incidental discovery of pituitary incidentalomas is increasing in frequency. The most common cause of a pituitary mass is a pituitary adenoma (90% of all pituitary masses); however, the differential diagnosis remains extensive. The challenge is to distinguish those that can or will cause morbidity/mortality from those that will not. Opinions on approaching management of these lesions vary. This article will review current data regarding the prevalence, natural history and potential morbidity associated with this entity and describe an epidemiological approach based on four questions: does an incidental mass put the patient at increased risk for an adverse outcome? Can individuals with treatable syndromes be accurately diagnosed? Is the treatment of these syndromes more effective in presymptomatic patients? And do the beneficial effects of presymptomatic detection and treatment of these patients justify the costs incurred? We recommend the following approach: recognizing that one size does not fit all and that the approach should be tailored to the needs of the particular case. If the mass was discovered on a computed tomography, an enhanced MRI is recommended. Detailed history and physical examination should be carried out to look for signs of functional or ‘subclinically’ functional tumor. Size and structure should be assessed, especially proximity to the optic chiasm. Laboratory evaluation with a serum prolactin for small tumors is cost effective, other lab testing is indicated if metabolic problems are present. Care should be taken to assess for hypopituitarism, clinically and biochemically, if the mass is large, that is, more than 1 cm, visual field testing is also recommended. Note that the vast majority of patients with pituitary incidentalomas that are microadenomas die with them, not from them.

**Keywords:** pituitary adenoma • pituitary incidentaloma • pituitary tumor

No technology is without its unintended consequences, consequences that can be for good or ill [1]. As stated by the 18th Century British philosopher David Hume, “it is impossible to separate the chance of good from the risk of ill.” Radiologic imaging is no exception. As imaging techniques have advanced in technical sophistication and ability to ‘see’ more clearly into previously hidden anatomic realms, identification of structures not consciously being sought has increased pari passu. These findings have been termed ‘incidentalomas’. This has been termed a ‘disease of modern technology’ [2], although incidentaloma is not so much a disease entity as it is a finding that may or may not represent a disease [3]. A pituitary incidentaloma is a mass unexpectedly detected through an imaging procedure, performed for reasons a priori unrelated to pituitary dysfunction or suspected dysfunction [2,4–6]. Naturally, the degree to which a tumor is unsuspected depends not only on severity of the clinical manifestations but also the clinical acumen of the physician [7]. Pituitary incidentalomas pose challenges to clinician and patient alike.

When confronting a pituitary incidentaloma for which the diagnosis is not certain, the challenge is to recognize and treat the small percentage of pituitary incidentalomas that do pose a significant risk, either because of their hormonal activity, mass effect or growth potential, while leaving the rest alone. The latter neither pose significant risk to a patient’s health nor warrant the risks of further diagnosis and treatment. Such evaluation may test not only the skills of the clinician but also the limits of biochemical testing. In addition, we must deal with the anxiety that comes from knowing about a ‘tumor’ that
might cause problems in the future [8,9]. A variety of authors have proposed different approaches to this evaluation, varying in the degree to which biochemical abnormalities are sought and in the extent and type of follow-up. Common to all approaches is a recognition not only of the importance of identifying potentially harmful conditions and of diminishing patient anxiety but also the costs, both financial and nonfinancial, of any evaluation [5,6,10–12]. As in other conditions, there is variation in clinical practice. This applies to the management of both incidental micro- and macro-adenomas. A vignette-based survey was conducted by endocrinologists in the USA and the UK [13].

- Case one: A 25-year-old woman has a history of chronic non-specific headaches. MRI was performed and showed a 5-mm lesion in the pituitary gland consistent with a microadenoma. Except for headaches, the patient is asymptomatic. She has normal menses, her physical examination is normal and she has no galactorrhea;

- Case two: A 49-year-old man with a history of diabetes mellitus and hypertension underwent MRI for complaints of multiple episodes of tingling in the right arm and leg. MRI showed a 1.5 cm lesion in the region of the sella, abutting the optic chiasm, and consistent with the diagnosis of pituitary macroadenoma. He is otherwise asymptomatic and has normal sexual function. There are no clinical signs to suggest either acromegaly or Cushing's disease. The endocrinologists were then quizzed about what tests/procedures they would usually obtain in such a case.

In this study, the median number (range) of tests usually or always ordered in case one was seven (0–16) and five (0–18) for UK and US responders, respectively. For case two, the numbers were eleven (4–17) and ten (0–19) for UK and US responders, although the differences were statistically significant, there was still considerable overlap. Similarly, the results for individual tests exhibited differences between UK and US practice, but there was considerable overlap. While UK endocrinologists would obtain hormone tests more frequently, the situation with radiology was reversed. In case one, US endocrinologists were significantly more likely to obtain a follow-up scan and to obtain one sooner – mean 9.1 versus 15.3 months (median 9 vs 12 months) for US and UK endocrinologists, respectively. In case two, US endocrinologists were more likely to obtain a follow-up scan (p = 0.082) and to obtain one sooner – mean 5.6 versus 7.6 months (median: 6 months for both) for US and UK endocrinologists, respectively. In case one, the patient would be referred to a neurosurgeon by 4.1 and 6.7% of UK and US endocrinologists, respectively. Case two would be referred to a neurosurgeon by 75.7 and 75.3% of UK and US endocrinologists, respectively (p = 0.93). The long-term morbidity and mortality associated with hormone-secreting pituitary tumors suggests that early identification and treatment is beneficial. Some authorities, therefore, recommend extensive biochemical screening in all patients with an incidentally discovered pituitary mass to detect hormonally active tumors, but these recommendations are controversial [4–6,11,14,15,201]. The wide variation in test-ordering behavior reflects an absence of consensus regarding the most appropriate approach and highlights the need for both research and debate regarding the most appropriate management of such incidentally discovered pituitary masses [13].

An epidemiological approach to this dilemma would be guided by answers to the following questions: does an incidental mass put the patient at increased risk for an adverse outcome? Can individuals with treatable syndromes be accurately diagnosed? Is the treatment of these syndromes more effective in presymptomatic patients? And do the beneficial effects of presymptomatic detection and treatment of these patients justify the costs incurred? In this review, we update our prior review of the literature and describe our approach to pituitary incidentalomas and propose an algorithm for diagnosis and management. Our effort began by systematically reviewing the literature.

**Narrative review of the literature**

We updated a prior review, focusing systematically on literature from 2000 to the present. We searched all articles in English using Google Scholar. Search terms included pituitary plus one of the following: incidentaloma, adenoma, tumor, nonfunctioning or hyperfunctioning. Additional databases searched included MEDLINE and the Cochrane Controlled Trials Register (1984–2009). Additional articles were identified from references in key articles. Of note, overall quality (strength) of the evidence from these articles was relatively poor when rated according to evidence-based medicine criteria. Specifically, there were neither randomized controlled trials nor nonrandomized controlled studies. In the absence of such research and an evidence-based guideline for management of such patients, endocrinologists will continue to disagree and approach this dilemma differently. That said, we offer our own approach. Pituitary incidentalomas are common and their course is usually benign. Approaches to evaluation and management include testing versus expectant management. This is best done if based upon size and function of the tumor.

**Frequency of pituitary incidentalomas**

Autopsy prevalence of pituitary masses at autopsy has ranged from 1.5 to 26.7% [6,15,16]. The largest single autopsy study involved 1000 unselected pituitary gland specimens; lesions were found in 17.8% [16]. A 2004 meta-analysis found the overall prevalence of pituitary adenomas to be 14.4% in autopsies and 22.5% in radiologic studies [17]. Most recently, Rittierdt and Horst had a series of 228 neuropathological autopsy cases, the frequency of incidentalomas in the series was seven out of 228, that is, 2.24% [18].

Pituitary adenomas have classically been divided by size: microadenomas are smaller than 10 mm, while macroadenomas are 10 mm and larger. In all autopsy studies, microadenomas predominate. There are relatively few population-based radiology studies. Three large studies of patients undergoing imaging for reasons unrelated to the pituitary found the prevalence to be 0.16–10.30% [19–21]. Using high-resolution computed tomography (CT) scanning in 107 women, Wolpert et al. identified pituitary lesions in 11.2% [22]. Of significance, the authors pointed to the noise
artifacts inherent in high-detail, thin-section soft-tissue scanning. Such artifacts can limit the ability to define reproducible patterns in different parts of the normal pituitary gland. This observation may account, at least in part, for the relatively high degree of interobserver variation. Hall et al. used MRI technology and identified pituitary lesions in 10% of normal volunteers [23]. For the purpose of the study, the diagnosis of a pituitary lesion required the agreement of two out of three radiologists reviewing the films. In fact, a pituitary lesion was identified in more than 40% by the criterion of the finding of a single radiologist. Dynamic MRI has been advocated as a more sensitive tool to detect pituitary adenomas; however, its lower reported specificity (88%) compared with conventional MRI may lead to the generation of false-positive results [24,25]. The few studies that have found a higher incidence of pituitary macroadenomas raise the question of selection bias; symptomatology related to microadenomas may have increased the probability of a patient undergoing a scan [26].

**Does an incidental mass put the patient at increased risk for an adverse outcome?**

There are four major types of potential morbidity: problems related to the nature of the etiology of the lesion itself, problems related to hormonal dysfunction, problems related to an expanding sellar lesion, and the anxiety caused by knowing that one is living with such a lesion [27]. This question addresses the natural history of pituitary incidentalomas and the answer involves inferences from several types of data. These include cross-sectional epidemiological studies of the prevalence of pituitary tumors and clinical syndromes associated with pituitary dysfunction or mass effect, and longitudinal studies of incidentalomas, nonfunctioning pituitary tumors in general and syndromes of pituitary dysfunction [11,28–37].

**Etiology**

The most common cause of a pituitary mass is a pituitary adenoma (90% of all pituitary masses); however, the differential diagnosis remains extensive (Box 1) [11,38]. The challenge is to distinguish those that can or will cause morbidity/mortality. However, morbidity from lesions other than pituitary adenomas is relatively uncommon. Pituitary metastases do occur, but uncommonly cause clinical manifestations, especially in the absence of a known primary tumor. Lymphocytic hypophysitis is usually clinically apparent [11,38].

**Frequency of hormonal dysfunction**

Microadenomas generally become symptomatic through hormonal hypersecretory syndromes, whereas macroadenomas may present with hypersecretory syndromes, hypopituitarism or neurological defects [11,38]. Each of these syndromes is associated with significant morbidity and mortality. Overall, the prevalence of symptomatic pituitary adenomas has been estimated to range from 0.9 to 94 cases per 100,000 people [39–41]. However, it is important to recognize that hormonal hypersecretion can be quite subtle or even clinically inapparent [42]. A recent study by Yuen et al. suggest that the presence of a pituitary incidentaloma is associated with a higher frequency of deficient growth hormone reserve [43]. Notwithstanding this observation, the high prevalence of incidental pituitary tumors at autopsy contrasts sharply with the relative infrequency of clinical syndromes of pituitary dysfunction. Estimates of clinical syndromes are shown in Table 1. For example, prolactin-secreting tumors account for the majority seen in most centers – approximately 60% [40,44]. Two screening studies for hyperprolactinemia have been performed in Japan. Miyai screened 10,550 adults (8450 males and 2100 females) and identified 40 with prolactin levels above 75µg/l; five out of 40 were found to have pituitary adenomas (three males and two females) and identified 40 with prolactin levels above 75µg/l; five out of 40 were found to have pituitary adenomas (three males and two females) for a point prevalence of 0.036% in males and 0.095% in females [45]. Note that the sensitivity of the test using a 75 µg/l cutoff is much less than 100%. Miyai screened 4803 adult males and identified three with prolactin levels above 500 µg/l for a point prevalence of 0.062% [46]. Note that prolactin levels of this magnitude are associated with macroadenomas (tumors ≥1 cm diameter). Prolactinomas may be associated with lower prolactin levels. Randall found that 16% of patients...
with proven prolactin-secreting tumors had basal prolactin levels below 50 µg/l; 45% had levels below 100 [47]. The typical upper limit of normal for serum prolactin is 15–20 µg/day. Thus, these studies underestimate the prevalence of hyperprolactinemia. In a Belgian study, the mean (a standard deviation) prevalence of pituitary tumors was 94 ± 19.3 cases per 100,000 population (95% CI; 72.2–115.8) [41]. Prolactinomas comprised 66% of those with pituitary tumors, with the rest having nonsecreting tumors (14.7%), somatotropinomas (13.2%) or Cushing’s disease (5.9%); 20.6% had hypopituitarism. Of note, 42.6% had macroadenomas, more than one would expect in a population-based study. Two older American studies also provide relevant data. During the period 1976–1980 in King, Pierce and Snohomish Counties (WA, USA), 78 women with prolactinomas were found for an annual incidence of 26 per 1,000,000 [48]. A prolactin level above 24 µg/l was used as the cut point. Similar results were observed in Olmstead County (MN, USA). During the period 1970–1977, the annual incidence of pituitary tumors was 7.1 per 100,000 population [49]. Prolactin-secreting tumors accounted for four out of 11 pituitary tumors for an annual incidence of 26 per 1,000,000.

Acromegaly (GH hypersecretion) is the second most commonly diagnosed disorder of pituitary hormone hypersecretion. Similar estimates of prevalence and incidence have been made based data from Olmstead County, Newcastle-upon-Tyne (UK), and Goteborg (Sweden) [49–51]. Another, considerably higher estimate, was reported from Germany [52]. Cushing’s disease (pituitary adrenocorticotropic hormone [ACTH] hypersecretion) is a rare disorder. Similar estimates of prevalence and incidence have been made based on data from Olmstead County, Japan, Spain, Denmark and Belgium [41,49,53–55]. Pituitary tumors may also secrete one of the glycopeptide hormones – thyroid stimulating hormone, luteinizing hormone, follicle-stimulating hormone, or their α- and β-subunits. Data related to the prevalence of glycopeptide hormone-secreting tumors is more limited. The prevalence of elevated levels of α-subunit in patients with ‘nonfunctioning’ clinically apparent tumors is 17–26% [56,57]. It should also be remembered that pituitary tumors may exhibit immunostaining for various pituitary hormones in the absence of clinical manifestations. Buurman et al. provided a detailed breakdown of 334 pituitary tumor cases that were found on 3048 autopsy cases – more than a third stained positive for prolactin, the rest stained for ACTH, gonadotrophins, α-subunit, growth hormone, and thyroid-stimulating hormone, respectively [58]. Large incidentalomas are associated with a high frequency of hypopituitarism [15,20,59]. However, the data in Table 1 indicate that clinically diagnosed hormone-secreting pituitary tumors are far less common than incidental pituitary microadenomas.

### Natural history of incidentalomas

Can individuals with treatable syndromes be accurately diagnosed?

**Imaging of the pituitary mass**

Studies correlating MRJ and histopathologic finding of pituitary masses are very limited. In one study correlating CT and surgical findings in 113 patients with proven pituitary adenomas,
CT scanning was found to have low specificity for pituitary lesions [64]. However, imaging techniques are useful in differentiating pituitary adenomas from other pathology, with MRI being described as more sensitive than CT for the detection of adenomas [65-66]. Connor and Penney described the specific MRI characteristics of different pathologies of the sella other than pituitary adenomas [67]. Meningiomas, metastasis, craniopharyngiomas, Rathke’s cleft cysts, arachnoid cysts, hypophysitis, abscesses, aneurysms, pituitary hemorrhage and hyperplasia may be differentiated from an adenoma, whereas germ cell tumors, chondrosarcomas, chordomas, gangliocytomas, pituitaryomas, melanomas and other tumors appear to be indistinguishable. The usefulness of such an evaluation lies in the fact that much sellar pathology, such as hypophysitis or pituitary hyperplasia, requires neither further evaluation nor surgical intervention. Pituitary carcinoma is mercifully rare [68]. CT has been reported to be superior in detecting calcifications, hence, helping in evaluating craniopharyngiomas and meningiomas [67]. Whether an MRI should be performed after finding an incidentaloma on CT scanning (or vice versa) is not clear. In a comparative study of 40 patients with a pituitary mass, it was found that CT scan and MRI were equivalent in the diagnosis of macro- but not micro-adenomas [69]. The higher sensitivity of MRI appears, thus, to be more useful in defining the lesion, as well as in assessing the extent of extrasellar extension, whereas CT is often used preoperatively to assess the sphenoid bone. However, these tests are by no means perfect. Roentgenographic techniques have a long and inglorious history of introduction prior to validation. Radiologic evaluation of the pituitary, especially in regards to microadenomas, is no exception [2]. In a study by Hall et al., in which high-resolution MRI scans of 100 normal volunteers were randomly mixed with scans of 57 patients with surgically confirmed Cushing’s disease, six out of the 57 patients had a hypointense lesion on preoperative MRI that did not correspond to the site of the microadenoma at surgery, resulting in a false-positive rate of 11% [24].

**Hormonal evaluation**

A variety of approaches have been advocated as strategies for baseline functional assessment. First, the importance of a careful history and physical examination cannot be overemphasized. Such a clinical assessment may direct evaluation in a more efficient manner than a ‘shotgun’ approach. However, one should not infer the absence of endocrine activity by the pituitary incidentalomas solely because of the absence of clinically recognizable signs and symptoms. Such clinical manifestations can be very subtle or absent. When a hormonal disorder is suspected clinically, the diagnostic evaluation can and should proceed [73–75]. However, in the absence of clear findings, that is, when the pretest probability of a particular disorder is low, biochemical evaluation is more challenging.

**Clinical epidemiological digression**

Diagnostic test performance characteristics are usually determined for patients with clinically apparent disease [76]. Inevitably, these tests will be less accurate when applied to patients lacking clinical features. Test sensitivity is likely to be lower than in study population from which the original characteristics were derived (spectrum bias); test specificity is also likely to be lower. Moreover, predictive value is dependent upon the prevalence of disease. Even a test with high sensitivity and specificity will, when used to detect a rare condition, falsely identify many non-affected individuals as having the disease. Experience with the low specificity of the overnight dexamethasone 1-mg suppression test is well known. Although less well known, but equally important, are the limitations of salivary cortisol for the diagnosis of Cushing’s syndrome. Initial studies reported sensitivities and specificities in the 92–100% and 93–100% ranges, respectively [77]. However, most studies were in research environments and with inpatients. Part of the variation results from different cut points used. However, lower specificities (and sensitivities) have been found in other studies [78]. In one study, as many as 40% of individuals older than 60 years of age with a variety of medical and social comorbidities had at least one abnormal late-night salivary cortisol result when two such tests were obtained [79]. Even apart from the relatively high prevalence of drug-induced hyperprolactinemia, there is the phenomenon of macroprolactinemia, either of which could lead to an unnecessary course of evaluation and treatment [80,81]. For example, of 11 patients with macroprolactinemia who underwent cranial imaging, two had findings consistent with microadenomas [80]. A retrospective analysis of 135 consecutive patients with hyperprolactinemia reveals a frequency of macroprolactinemia of 42.2%. While the macroprolactinemia accounted for the abnormal prolactin level, a third of these patients presented with signs and symptoms of hyperprolactinemia. Moreover, approximately half of patients had MRI abnormalities. The optimal strategy for hormonal evaluation of a patient with an incidentally discovered pituitary mass is unclear and remains controversial. Regardless of the approach used, it should be tailored to what is available; tests should be chosen based on their performance characteristics in the laboratories available to the clinicians ordering the test.

**Is the treatment of these syndromes more effective in presymptomatic patients?**

Hormone-secreting pituitary tumors are associated with morbidity and premature mortality. Even in the absence of some of the classic symptoms of prolactin excess, such as galactorrhea and menstrual irregularity in women, and galactorrhea (less common) and decreased libido or impotence in men, hyperprolactinemia may cause anovulation and infertility. In addition, hyperprolactinemia has been associated with osteoporosis,
a disorder with a major impact on morbidity and mortality. Growth hormone-secreting pituitary adenomas are usually larger than 1 cm in diameter when the clinical diagnosis of acromegaly is made because of the slow progression of the clinical manifestations; most cases are diagnosed when they are macroadenomas. Growth hormone hypersecretion from pituitary tumors has been observed in the absence of clinical findings [3]. These observations suggest that early diagnosis might be of benefit. These findings indicating a benefit of early diagnosis suggest the importance of case finding.

**Do the beneficial effects of presymptomatic detection and treatment of these patients justify the costs incurred?**

A common concern clinicians face when dealing with a patient harboring a pituitary mass is the possibility of underdiagnosing subclinical disease. This may partially explain the frequent ordering of numerous endocrine tests during evaluations [13]. This concern is felt by the patients as well. In fact, when sensitivity analyses were performed in a cost–effectiveness analysis (see later), the model was highly sensitive only to the patient’s psychological discomfort associated with the diagnostic uncertainty. As baseline psychological discomfort increased, testing became more cost effective. Within plausible limits, cost of testing, complication rate of surgery and prevalence of hormonal hypersecretion had little effect on the results [10]. Cost–effectiveness analyses can be performed when there is a measure of the outcome of actions (either individual or treatment interventions) in terms of their health impact, combining the quantity and quality of life. One such measure is the quality-adjusted life-year (QALY). If an action gives a person an extra year of healthy life expectancy, this counts as one QALY. If an action gives a person an extra year of unhealthy life expectancy (partly disabled or in some distress), it has a value of less than one. Death is rated at zero.

One formal cost–effectiveness analysis of management strategies for incidentally discovered pituitary microadenomas has been performed [10]. The three screening/follow-up strategies included single prolactin level, endocrine panel to detect prolactin, growth hormone and ACTH excess, and periodic MRI follow-up, which were compared with watchful waiting. They concluded that the most cost-effective strategy, after clinical assessment, was a single test for prolactin (US$1428/QALY). The limited panel of endocrine tests was slightly more effective but less cost effective ($69,495/QALY) and repeat MRI was both less effective in terms of total QALYs and more expensive (> $100,000/QALY). A greater appreciation of ‘subclinical’ cortisol excess and its increased prevalence in certain conditions, for example, the metabolic syndrome, poorly controlled diabetes and osteoporosis with vertebral fractures, suggests a need for another look at screening for this entity in patients with incidental pituitary masses. Most of the data on autonomous glucocorticoid hypersecretion derive from patients with adrenal lesions. Data on the frequency of the analogous autonomous (or semiautonomous) ACTH hypersecretory state are unknown. Catargi et al. reported that subclinical Cushing’s signature is present in 2% of a population of overweight, poorly controlled diabetic patients [82]. Of the four patients with the definitive diagnosis of Cushing’s syndrome, three had pituitary disease. By contrast, Newsome et al. found a prevalence of below 1% (one possible case out of 171 patients) [83]. Nagai et al. reported improvement in glucose and blood pressure control in a diabetic woman with subclinical Cushing’s disease after transphenoidal surgery, and a similar result was observed by Contreras et al. [84,85].

**Recommendations & reflections**

Our recommendations are summarized in the algorithm in **Figure 1.** The level of evidence mentioned in this paragraph is obtained from the Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001). In the case where the mass was discovered by CT, obtaining a MRI might lead to a specific diagnosis, obviating the need for further work-up (level C). If the mass is larger than 10 mm, tests for hormonal excess and deficiency, as well as visual-field and acuity testing, are required. It should be recognized that assessment of visual fields by confrontation is of much lower sensitivity than more formal methods, for example, Goldmann perimetry. In addition, neurologic examination for findings potentially related to a pituitary mass, for example cranial nerve abnormalities, should be performed (level B). In the absence of visual/neurologic or hormonal dysfunction and when there appears to be no immediate threat to the optic chiasm or other critical structures (level B), close follow-up with MRI every 6 months for 1 year, then annually for 1–2 years is prudent in view of the modest propensity of some of these tumors to expand in size (level D). Patient preference for surgical removal or even a trial of medical therapy should be considered. Assuming stability in lesion size, the imaging interval can be lengthened, perhaps doubled each time. Parameters for follow-up also depend upon the size of the macroadenoma; a 1.1-cm lesion would be handled differently than a 1.9-cm lesion. Consideration for surgery would depend primarily on the presence or threat of neurologic effects of the lesion. A 1.1-cm (non-prolactin-secreting) lesion reaching the optic chiasm on MRI may require surgery even without hormonal abnormalities or visual field defects, whereas a larger lesion not threatening visual abnormalities but causing gonadotropin deficiency in an elderly (and already estrogen-deficient) woman may be followed conservatively. For microadenomas, a serum prolactin represents the most cost-effective test to be obtained (level B). Further hormonal testing, specifically for subclinical Cushing’s, will be dictated by the presence of features of the metabolic syndrome or other clinical suspicion (level D). Where the pretest probability for Cushing’s disease is higher, as in these conditions, it may be prudent to screen for Cushing’s disease. In patients without hormonal abnormalities, expectant management (i.e., additional laboratory evaluation only if symptoms develop) can be adopted (level D). Depending upon the size of the lesion and patient preferences, we may repeat the MRI once (level D).

It is clear that pituitary incidentalomas are a heterogeneous entity and more definitive recommendations await further research, particularly on the long-term outcomes of different approaches.
Incidentally discovered pituitary masses: pituitary incidentalomas

**Figure 1. Simplified algorithm for the evaluation and management of a patient with an incidentally discovered pituitary mass.** The inset illustrates the algorithm for expectant management. Reproduced with permission from [11].
Pituitary incidentalomas typify the fact that incidental findings by their very nature pose a risk of overdiagnosis and overtreatment. Although most pituitary incidentalomas are of no lasting significance beyond the anxiety they produce indirectly (not a trivial concern), some are clinically significant, and inadvertently leaving them alone might damage the patient’s health. Therefore, detection of an incidentaloma necessitates a conscious and conscientious decision regarding its management. Ideally, this decision/recommendation should be based on careful consideration of the risks and benefits of each diagnostic and therapeutic step, as well as individual patient preferences [86]. The level of a patient’s anxiety will undoubtedly influence the extent of testing during the evaluation process and may also influence management decisions as some patients will request or demand surgical removal irrespective of the nature of the mass.

The optimal strategy for hormonal screening of a patient with an incidentally discovered pituitary mass is unknown. Review of the endocrinologic literature supports the view that such patients are at somewhat, albeit low, increased risk for pituitary-related morbidity and mortality, indicating a benefit of early diagnosis for at least some of the disorders. From a clinical perspective, our ability to determine accurately those at increased risk among the vast majority who are not at increased risk is relatively poor. Given the limitations of diagnostic tests, effective hormonal case finding requires a sufficiently high pretest probability to limit the number of false-positive results. This condition is met to varying degrees in the patient with a pituitary mass. Subjecting patients to unnecessary testing and treatment carries its own set of risks [87]. Initial costs aside, testing may result in further expense and harm as false-positive results are pursued. For example, quality of transsphenoidal surgery varies widely, and complication rates are not zero. This pursuit of test after test has been termed the cascade effect, a “chain of events (which) tends to proceed with increasing momentum, so that the further it progresses the more difficult it is to stop” [88]. The extensive evaluations performed in some patients with incidentally discovered masses may reflect the unwillingness of many physicians and patients to accept uncertainty, even in the case of extremely unlikely diagnoses [89]. Notwithstanding these considerations, and pending the accumulation of better evidence on which to base our decisions, we believe that the scheme outlined in Figure 1 and modified based on patient’s overall condition and preferences, represents a prudent approach.

Expert commentary & five-year view
Pituitary incidentalomas will continue to become more common with the advancing radiographic technique [90–93]. They are beginning to be described on PET scans and we can anticipate more diagnostic dilemmas. Over the next 5 years, there will be advances on both the basic science and clinical fronts. While, thus far, differences between incidentalomas and clinically evident non-functioning tumors in expression of proliferation markers have not been observed, further work may identify factors that predict growth potential [94]. On the clinical front, the major advance will be the development of a pituitary incidentaloma registry. The likelihood that there will be randomized controlled trials is virtually nil and we will have to rely on good observational studies. Collaboration among the various groups that have pituitary tumor registries. Disease-specific registries are becoming more common in endocrinology (beyond diabetes registries) and they will facilitate observational studies [95–97]. There may be a study to determine the prevalence of hormonal dysfunction associated with incidental microadenomas. This would enable a better analysis of management strategies. Finally, there will be more attention paid to the ethical and medical–legal issues involved when incidental findings are identified. This is true for research studies, but also in clinical practice [98–100]. Stone in a very perceptive commentary in the New England Journal of Medicine wrote [101]:

“The issue of what to do regarding incidentalomas is not simple. Any discussion must acknowledge the thousands of lawsuits in the United States each year that result from a physician’s failure to act on some early evidence of a problem that ultimately leads to an adverse outcome. Guided in part by fears of lawsuits, clinicians tend to order additional tests. All too often, these tests do not result in clinical clarity, diagnostic certainty, or patient satisfaction. Caught in the same bind, radiologists are inclined to suggest additional tests and to dictate in their reports ‘cannot exclude…’ ‘need to rule out…” ‘consistent with…” and ‘clinical correlation required’, implying that a sinister cause of the finding might be discovered, if only the problem were investigated with sufficient vigor. This cycle of disclaimers and protectionist test-ordering passes the buck between clinician and radiologist, adds to the financial demands on payers, heightens patients’ worry, and yet offers little insight into the appropriate level of concern. Since we cannot ‘unknow’ the fact of an incidental finding, we need information on reasoned approaches to the findings once they occur. Defining rational approaches to incidentalomas would have important implications for society’s views of medicine: do practitioners use expensive resources responsibly, apply evidence rigorously, and validate the benefits of new technology? In the coming years, imaging techniques will grow more sensitive and, likely, less specific in many cases. Imaging can help us look, but both clinical correlation and translational science are required before any technique can help us see with optimal focus.”

We wish we could be sanguine regarding the prospects of evaluation of technology before widespread adoption. Prediction is very difficult, especially about the future. So said the Danish physicist Niels Bohr. Whether or not our predictions represent only wishful thinking tinged with cynicism will be borne out by time.

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Key issues

- The frequency of pituitary incidentalomas is increasing because of advancing technology and increasing numbers of radiological examinations.
- Pituitary incidentalomas usually follow a benign course; individuals die with them and not from them.
- If the mass was discovered on computed tomography, an enhanced MRI is recommended.
- Detailed history and physical exam should be carried out to look for signs of functional or 'subclinically' functional tumor.
- Size and structure should be assessed, especially proximity to the optic chiasm.
- Laboratory evaluation with a serum prolactin for small tumors is cost effective, other laboratory testing is indicated if metabolic problems are present.
- Care should be taken to assess clinically and biochemically for hypopituitarism if the mass is large, that is, 1 cm and larger. Visual-field testing is also recommended.
- One size does not fit all. The approach should be tailored to the needs of the individual.

References

Papers of special note have been highlighted as:

• of interest


• Alternative viewpoint concerning the extent of hormonal evaluation.


• Only cost–effectiveness analysis to have been conducted. Of note, the analysis was most sensitive to the patients anxiety related to the presence of a mass. Other factors had little impact.


• Critical study illustrating the problems of specificity and sensitivity of MRI, as well as interobserver variation.


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Review


Rare study of pituitary tumor growth rates.


Although this study found no difference between non-functioning tumors that had been diagnosed clinically and incidentalomas, this area of investigation is one of the more promising.


Affiliations
• Dima Abdelmannan, MD
Endocrinology Section 111(W), Louis Stokes Department of Veterans Affairs Medical Center, 10701 East Boulevard, Cleveland, OH 44106, USA
and
Division of Clinical and Molecular Endocrinology, Case Western Reserve University School of Medicine, Cleveland, OH, USA
dima.abdelmannan@va.gov

• David C Aron, MD, MS
Division of Clinical and Molecular Endocrinology, Case Western Reserve University School of Medicine, Cleveland, OH, USA
and
Associate Chief of Staff/Education, Co-Director
VA Health Services Research and Development Service Center for Implementation Practice and Research Support, Education Office 14 (W), Louis Stokes Department of Veterans Affairs Medical Center, 10701 East Boulevard, Cleveland, OH 44106, USA
Tel.: +1 216 421 3098
Fax: +1 216 231 3427
david.aron@va.gov