Adrenal Masses in the Cancer Patient: Surveillance or Excision

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ABSTRACT

An increasing number of patients with a history of solid organ malignancy now undergo surveillance imaging as part of their follow-up or for evaluation of other conditions. This imaging has led to both greater identification of asymptomatic adrenal masses and subsequent confusion among clinicians regarding the evaluation and treatment. Although established algorithms exist for treating such “incidentalomas” in otherwise healthy patients, the most effective way to do so in patients with known prior or concurrent malignancies is unclear. In this review, we explore methods of biochemical testing in such patients and discuss the role of imaging techniques in their ability to differentiate benign versus malignant lesions. In this population, we examine the increasing use of biopsy and discuss current data on both surveillance and resection of lesions based on their identity. Finally, we propose an algorithm to aid the clinician in evaluating and treating these complex patients efficiently.

INTRODUCTION

Patients with a personal history of solid organ malignancies generally undergo lifelong surveillance for tumor recurrence or metastases. A major component of cancer surveillance includes imaging such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scans. The technology for radiologic imaging is vastly improved; therefore, the prevalence of incidentally discovered tumors is increasing. The adrenal gland is peculiar because it is not only a common site for metastases, but it frequently harbors incidental (nonmalignant) masses. These masses represent a diagnostic challenge for physicians and a major source of anxiety for the patient. In this review, we discuss the evaluation and management of incidentally discovered adrenal masses, with emphasis on patients with a personal history of cancer.

It is our objective to inform the clinician about the nature of incidentalomas in patients with a history of malignancy and suggest cost-effective and efficient algorithms for managing such patients based on available clinical evidence.

PREVALENCE OF ADRENAL MASSES

Single adrenal masses (incidentalomas) are found serendipitously in 2%–9% of all abdominal CT scans [1, 2]; however, autopsy studies show prevalence rates of 7.3%–8.7% for adrenal masses [3]. Of particular interest, Kloos et al. [2] noted that 32%–72% of incidentally discovered masses in patients with a history of cancer were metastases. Lenert et al. [4] also found that 52% of adrenal masses in 91 patients with a recently diagnosed extra-adrenal malignancy were metastatic, whereas 48% were primary adrenal lesions, including pheochromocytoma and cortical adenomas. The
median time from cancer diagnosis to identification of adrenal metastases was 2.5 years, although adrenal metastases have been discovered up to 22 years after initial treatment of primary tumors [5].

**Biochemical Evaluation of the Patient with an Adrenal Mass**

Appropriate biochemical evaluation of patients with adrenal masses is necessary to prevent inappropriate—and potentially dangerous—therapy, especially in a patient with pheochromocytoma. Therefore, we recommend that all patients with adrenal masses undergo biochemical evaluation for cortical or medullary hyperfunction prior to further imaging, biopsy, or therapy.

**Adrenal Cortical Hyperfunction**

Clinical evidence of adrenal cortical hyperfunction includes hypertension, hypokalemia, sudden weight gain, truncal obesity, and progressive myopathy. However, these clinical symptoms may be masked (and thus less reliable) in the cancer patient because of underlying cancer symptoms. Initial studies should include serum potassium, chest radiography in all patients, and mammography in women. Screening patients for excess cortisol production should include the measurement of 24-hour urinary-free cortisol (UFC) and a low-dose (1 mg) dexamethasone suppression test. Adequacy of timed urine specimens should be confirmed by measuring urinary creatinine excretion. Patients with basal UFC excretion greater than 3 times the upper limit of normal can be assumed to have hypercortisolism; however, confirmation of autonomous cortisol hypersecretion should be confirmed by a dexamethasone suppression test. This is because a 5.6% false-negative rate has been reported for 24-hour urinary-free cortisol measurement [6]. Furthermore, some patients with subclinical Cushing’s syndrome may not have elevated urinary cortisol levels. Salivary cortisol levels obtained at midnight are emerging as the most sensitive test for the diagnosis of hypercortisolism.

The low-dose dexamethasone suppression test is relatively sensitive in identifying patients with hypercortisolism. Traditionally, a plasma cortisol level <5 μg/dl after overnight dexamethasone suppression is normal, whereas values of 5–10 μg/dl are equivocal. These levels are associated with a 10%–15% false-positive rate, and recent recommendations call for a decrease in cutoff values to <1.8 μg/dl [7, 8]. Screening for adrenal cortical hyperfunction should also include the measurement of plasma aldosterone concentration (PAC) and estimation of plasma renin activity (PRA) to determine the presence of primary hyperaldosteronism. In addition to documenting an elevated ratio of plasma aldosterone to plasma renin activity (>20), the plasma aldosterone should be significantly elevated (>15 ng/dl) [9]. Weinberger and Fineberg [10] report that a PAC-to-PRA ratio of >30 plus a PAC level over 20 ng/dl were associated with a sensitivity and specificity of 90% and 91%, respectively, for the diagnosis of primary hyperaldosteronism.

**Adrenal Medullary Hyperfunction**

Measurement of serum and/or urinary concentrations of catecholamines and their metabolic products is the mainstay of screening for adrenal medullary hyperfunction. Although measurement of 24-hour urinary levels of catecholamines and their metabolites has been the test of choice for decades, it remains an inconvenient test for many outpatients. Furthermore, new evidence now suggests that a single measurement of plasma metanephrines is as sensitive as urinary studies [11, 12–14]. Blood samples should be collected using venous catheters in patients who have been sitting or supine for at least 5 minutes to reduce the incidence of false-positive results. In addition, overnight fasting, abstinence from caffeinated beverages, and avoidance of acetaminophen for 5 days prior to blood sampling are recommended.

**Radiologic Diagnosis**

Benign adrenal masses consist predominantly of intracellular lipid (composed mainly of cholesterol, fatty acids, and neutral fat), whereas malignant lesions do not contain much intracytoplasmic fat. This property has been exploited to differentiate adrenomas from nonadenomas on CT and MRI scanning. Both CT and MRI can reliably characterize intrallesional fat content. Korobkin and Francis [15] showed an inverse linear relationship between the intracytoplasmic fat content of an adrenal adenoma and the CT density value. Nonadenomatous lesions have higher CT density values because their cytoplasm is relatively lipid-poor. A CT scan attenuation value <10 Hounsfield units (HU) or visual detection of a diffuse decrease in relative signal intensity (relative to the spleen) indicates a lipid-containing benign adenoma with a specificity of more than 95% and a sensitivity of nearly 80% [16].

To determine the relevant threshold values on contrast-enhanced CT scans, investigators have examined the rates of washout of contrast dye as a means of characterizing adrenal masses. The rate of washout of intravenous contrast agents is slower in nonadenomas compared with adenomas. Korobkin et al. [17] noted that adenomas washout rates were 51% at 5 minutes and 70% at 15 minutes, with sensitivity and specificity of 96%. Updating previous work, Szolar and Kammerhuber [18] and Szolar et al. [19] retrospectively reviewed CT scan results of patients with a
total of 73 histologically confirmed masses. These included 24 adenomas, 11 carcinomas, 17 pheochromocytomas, and 21 metastases in 67 patients. Each patient underwent a non-enhanced scan, followed by 1- and 10-minute delayed contrasted studies. Sensitivity and specificity of 100% in differentiating adenomas from other lesions were achieved by applying absolute and relative percentage washouts of 50% and 40%, respectively, at 10 minutes [18, 19]. Similar results have been achieved in another analysis using newer multidetector-row CT techniques with contrast washout [20]. We recommend the use of dedicated CT protocols with washout analyses in the evaluation of incidental masses. Although these techniques are useful in excluding malignancy within an adrenal lesion, they have little value in confirming adrenal malignancy.

MRI
MRI also takes advantage of the aforementioned lower signal intensity in lipid-rich adrenal adenomas compared with lipid-poor lesions such as metastases; however, there is significant overlap using this technique [15]. Chemical-shift MRI takes advantage of the different resonance frequency peaks for the hydrogen atom in water and lipid molecules to identify adrenal adenomas. Mitchell et al. [21] demonstrated a relative loss of signal intensity in 26 of 27 adrenal adenomas (95%), compared with 12 metastases with no loss of signal intensity. In a series of 229 histologically confirmed adrenal masses (though only eight metastases), Honigshnabl et al. [22] noted sensitivity of 89% for differentiating benign and malignant lesions, with a 99% specificity. Others have reported similar accuracy using this technique [23–27]. Therefore, we recommend contrast-washout CT or chemical-shift MRI as the primary imaging technique to identify malignancy in adrenal lesions. MRI is particularly useful for lesions that are indeterminate or in patients who cannot tolerate iodine-based contrast agents.

PET
PET may now be the most commonly used surveillance tool in patients with cancer. The most common technique is [18F]fluorodeoxyglucose/positron emission tomography (FDG-PET), which relies on uptake of FDG by metabolically active cells as a method of identifying metastatic lesions. Numerous studies report high sensitivity and specificity for PET in identifying metastatic and recurrent cancer. In an early study, Boland et al. [28] reported 100% sensitivity and specificity for PET in differentiating adrenal masses in patients with known primary cancers as benign or malignant. In addition, Erasmus et al. [29] studied 27 patients with 33 adrenal masses in the context of known bronchogenic carcinoma and found PET to be 100% sensitive and 80% specific for the identification of metastatic disease. Others have demonstrated sensitivity and specificity of 95% and 92%, respectively, for PET in patients with known malignancies [30]. In an effort to avoid false-positive results from adrenal adenomas (which also take up FDG to a varying degree), several studies have modified PET criteria for what constitutes a positive lesion. Yun et al. [31] defined lesions with subjective uptake greater than or equal to the liver as positive for metastasis and less uptake than the liver as negative. Using these criteria, they reported 100% sensitivity and 94% specificity in 50 adrenal lesions. Using similar, liver-based criteria, Kumar et al. [32] reported a sensitivity and specificity for malignancy of 93% and 90%, respectively, in 94 patients. Interestingly, the false-negatives in this study were a large, necrotic metastasis, a 2.4-cm hemorrhagic lesion, and three lesions of approximately 1 cm, whereas the false-positives included a pheochromocytoma and three adenomas.

To further improve the sensitivity, PET/CT imaging has emerged as a powerful tool in evaluating adrenal masses. Metser et al. [33] retrospectively reviewed 175 masses by PET/CT and noted that PET misclassified 9 of 175 lesions, whereas the addition of nonenhanced CT data reduced this number to 3 of 175 (the six lesions were all adenomas). Blake et al. [34] showed similar excellent results with PET, and the addition of contrast-washout CT data yielded 100% sensitivity and specificity. Both studies were retrospective and were limited by low numbers of histologically confirmed lesions; however, they suggest that PET/CT may have great potential for improving the sensitivity accuracy of adrenal imaging.

SIZE
The size of an adrenal mass has long been used as a surrogate for primary adrenal malignancy. Primary adrenal cortical carcinoma, although rare (1 in 4,000 adrenal tumors), is more common in larger adrenal lesions. In fact, adrenal cortical carcinoma accounts for 2% of tumors less than 4 cm, 6% of tumors 4.1–6 cm, and 25% of tumors greater than 6 cm. Therefore, we recommend surgical resection of any lesion greater than 4 cm, based on its potential for malignancy, assuming the patient is an appropriate surgical risk [35].

PERCUTANEOUS BIOPSY OF THE ADRENAL
Although CT and MRI imaging can characterize adrenal masses as benign adenomas, masses suspected to be metastases can be confirmed by percutaneous biopsy in patients with a known primary extra-adrenal neoplasm and no other evidence of metastatic disease. Percutaneous fine-needle aspiration biopsies of the adrenal that show malignancy
have a positive predictive value of 100% and a negative predictive value for malignancy of 92%, with complication rates from 8%–13%, although most are mild and self-limiting [36, 37]. Unlike the high (>90%) accuracy for cytologic distinction between adrenal adenomas and metastases, histologic distinction between benign adrenal lesions and primary malignant adrenal lesions is difficult, with sensitivity ranging from 54% to 86%. Thus, we do not recommend percutaneous aspiration biopsy to differentiate an adrenal adenoma from a primary adrenocortical carcinoma.

**The Patient with a History of Malignancy**
The evaluation of adrenal masses in patients with a history of malignancy should be similar to other patients with incidentally discovered adrenal masses. Based on the evidence, we recommend biochemical evaluation as the initial step. This can then be followed by adrenal-specific imaging (noncontrast CT followed by contrast CT with washout for high-attenuation [>10 HU] lesions). If these results are equivocal or the patient cannot tolerate CT, we recommend imaging with PET or MRI depending on institutional availability and expertise. Biopsy should be reserved for masses that cannot be adequately characterized by imaging or that appear malignant on imaging studies. An alternative to the above approach is in patients whose primary malignancy can be effectively staged with PET imaging (such as lung cancer). Adrenal mass evaluation by PET is usually adequate to answer the question of metastatic disease, and further imaging should not be required. If PET is indeterminate or negative despite a strong suspicion of metastatic disease, it should be supplemented with contrast CT with contrast washout. CT-guided adrenal biopsy is an important diagnostic tool for indeterminate masses. Based on the information above, we propose and currently employ the algorithm shown in Figure 1 for the evaluation of incidental adrenal tumors, fully realizing the influence of institutional resources, preference, and local expertise on this choice.

**Management of the Solitary Adrenal Metastasis**
Although adrenalectomy is the standard of care for functioning adrenal masses, controversy still surrounds the optimal management of isolated adrenal metastases. There is accumulating evidence that resection of isolated adrenal metastases offers a survival benefit. Among lung cancers, a review of 11 reports for a total of 32 patients in the small subset of lung cancer patients whose only metastatic focus seemed to be adrenal showed a median survival of 2 years in patients with resection, with one third surviving greater than 5 years [38]. In a single-institution review of all adrenalectomies performed for both synchronous and metachronous disease, Sarela et al. [39] noted a median survival of 28 months. In that study, a disease-free interval (DFI) of greater than 6 months between resection of the primary cancer and discovery of metastatic disease predicted improved survival. Lenert et al. [4] found the median survival after adrenalectomy for metastasis was 3.4 years. These results confirm the prior experience of Kim et al. [40] and Lo et al. [41], who recommended aggressive treatment in patients who underwent complete resection of primary lung tumors and had a DFI >6 months prior to identifying adrenal metastases. An important caveat is that many of these studies consist of highly selected patients. Adrenal metastases from lung cancer and melanomas represent the bulk of these patients. There is no evidence supporting adrenalectomy for tumors with an unknown primary source. The evidence supports a laparoscopic approach for the resection of adrenal masses in the absence of local invasion. This can be accomplished without compromising the safety or adequacy of resection in properly selected patients [42]. However, patients with confirmed or suspected adrenal cortical carcinoma that require a more radical excision and lymphadenectomy may be best served by open adrenalectomy [43, 44].

**Natural History and Surveillance for Adrenal Incidentalomas**
Patient anxiety and expense are significant disadvantages associated with repeated imaging and biochemical testing in patients with incidental adrenal tumors. Therefore, a short discussion of the nature, frequency, and intensity of surveillance is warranted. Barzon et al. [44] evaluated the long-term (median, 4 years; range, 2–10 years) clinical, hormonal, and morphological outcomes of 75 patients with apparently benign adrenocortical incidentalomas to identify features predictive of progression of the adrenal disease. During follow-up, none of the incidentalomas proved to be malignant, but nine glands increased in size, and a new mass appeared in the contralateral gland in two patients. The estimated cumulative probabilities of adrenal mass enlargement and hyperfunction during long-term follow-up were 8% and 4%, respectively, after 1 year, 18% and 9.5% after 5 years, and 22.8% and 9.5% after 10 years. Serial CT scanning has also been recommended at 3-month intervals during the first year and annually thereafter; however, the data to support this strategy are scant. Barry et al. [45] examined the outcomes of 231 patients with adrenal incidentalomas who underwent surveillance for a mean duration of 7 years. Ninety-one patients had at least
one repeat CT scan during surveillance, and only 4 (4.4%) of these 91 patients had more than a 1-cm increase in the diameter of the adrenal mass during follow-up. All four lesions were pathologically benign upon resection. No patient developed adrenal hyperfunction or adrenal malignancy during follow-up, suggesting that conservative management of incidentalomas 4–6 cm in diameter is appropriate if the patient is not a candidate for surgery or the CT appearance of the incidentaloma is diagnostic or highly suggestive of a benign lesion (e.g., adrenal cyst, adrenal hematoma, or adrenal myelolipoma).

Recently, Bernini et al. [46] followed 115 patients for a median of 4 years (range, 1–7 years) with adrenal incidentalomas and normal endocrine profiles (or subclinical mild alterations). It was noted that many subclinical hormonal changes regressed while new ones emerged, with no significant risk factors for either. Furthermore, mass changes in the lesions were unrelated to changes in hormonal profiles, and no malignancies developed. Recommendations from this study were that in the case of a benign lesion with a normal or near-normal endocrine evaluation, follow-up CTs should be obtained every 2 years, with hormonal profiles every 3 years, for a total of 7–10 years [46]. Based on these studies described, we recommend prolonged surveillance for tumors >3 cm. Patients with smaller tumors and no biochemical or clinical evidence of hyperfunction may benefit from limited surveillance (1–2 years); however, the exact duration is undetermined. This may be a moot point in patients with a history of malignancy because many cancer surveillance protocols are more intense and frequent. Therefore, we recommend that such surveillance be expanded to include images of the adrenal glands by PET or CT.

**CONCLUSION**

Incidentally discovered adrenal masses are more prevalent and present unique challenges in patients with a personal history of cancer. The combination of sensitive biochemical tests and high-resolution imaging accurately identifies metastatic disease in most of these patients. We anticipate that future studies will establish comprehensive algorithms that determine the appropriate methods of surveillance for each tumor type. There is also a need to further delineate the role of PET/CT and the use of novel molecular imaging techniques. Surgical resection has been the mainstay of therapy for metastatic adrenal lesions. However, there is mounting interest in the use of percutaneous ablative techniques for these le-

![Figure 1](http://theoncologist.alphamedpress.org)
sions, especially in patients who may be poor candidates for surgery [47, 48]. The safety and efficacy of these techniques remain to be determined.

REFERENCES


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DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors indicate no potential conflicts of interest.


