Review Article

Current concepts in the management of adrenal incidentalomas

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Abstract

Adrenal tumors are among the commonest incidental findings discovered. The increased incidence of diagnosing adrenal incidentalomas is due to the widespread availability and use of noninvasive imaging studies. Extensive research has been conducted to define a cost-effective diagnostic and therapeutic protocol to guide physicians in managing incidental adrenal lesions. However, there is little consensus on the optimal management strategy. Published literature to date, describes a wide spectrum of treatment options ranging from excision of all adrenal lesions regardless of the size and functional status to extensive hormonal and radiological evaluation to avoid surgery. In this review, we present a comprehensive overview of the presentation, evaluation and management of adrenal incidentalomas. Additionally, we propose a management algorithm to optimally manage these tumors.

Key Words: Adrenal cortex, adrenal medulla, aldosteronomas, carcinoma, incidentalomas, pheochromocytoma

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Received: 29.09.2011, **Accepted:** 08.01.2012

INTRODUCTION

Adrenal incidentalomas (AI) are an adrenal mass lesion >1 cm in diameter discovered during testing or treatment for conditions unrelated to any suspicion of adrenal disease.[1] Adrenal tumors are among the commonest incidental findings discovered. Autopsy studies reveal that an adrenal tumor is found in 3% of people older than 50 years of age.[2]

The increased incidence of diagnosing adrenal incidentalomas is due to the widespread availability and use of noninvasive imaging studies. Prevalence of diagnosing incidental adrenal masses via computerized tomography (CT) has been estimated to be 0.35-4.4%.[3] With similar sensitivities (90-100%) and specificities (70-80%) MRI and CT are equally efficacious in diagnosing adrenal lesions. Autopsy studies examined the frequency of incidental adrenal nodules; the overall frequency of adrenal adenomas in 87,065 autopsies was reported to be 6% (range 1-32).[1]

Management of incidental adrenal tumors carries great impetus as some of these lesions can be adrenal cortical carcinomas which carry a high mortality rate. The other clinical concern is hormone overproduction due to pheochromocytoma, aldosteronomas and subclinical hypercortisolism which carries increased morbidity if untreated.[4]

A meta-analysis revealed that the most common etiologies for AI were as follows: 74% nonfunctional adenomas, 7% subclinical Cushing's syndrome (CS), 1.2% aldosteronomas, 4.7% pheochromocytoma, 4.8% adrenocortical carcinoma (ACC) and 2.3% metastatic lesions.[5] In this review, we present a comprehensive overview of adrenal incidentalomas and the current concepts in their management.

Access this article online	
Quick Response Code:	Website: www.urologyannals.com
	DOI: 10.4103/0974-7796.102657

Adrenal cortical tumors

The cortex makes up about 10% of the adrenal gland. Table 1 illustrates the possible differential diagnoses for adrenal incidentalomas. Adrenal cortical tumors include benign adenomas, nodular hyperplasia and adrenal cortical carcinoma (ACC). Both benign and malignant masses can be functional, secreting excess of mineralocorticoids, glucocorticoids and adrenal androgens. Studies have shown that cortisol and aldosterone producing tumors are likely benign. On the contrary virilizing tumors are likely to be ACCs.[1]

Adrenal cortical adenomas

The majority (74%) of AI are nonhypersecretory adenomas. However, 18-20% of patients undergoing adrenalectomy for presumed nonsecretory adenomas present with adrenal insufficiency. This implies that nonsecretory tumors are functional at a subclinical level.[6,7] Subclinical Cushing's syndrome (SCS) is the most common hormonal abnormality seen in patients with AI, with a prevalence of 5-47%.[8,9] Patients with SCS lack the clinical signs of overt Cushing's syndrome (CS). However, they are at increased risk for hypertension, diabetes, dyslipidemia, bone loss and obesity.

The incidence of primary aldosteronism is increasing compared to reports in the past.[10] The prevalence of mineralocorticoids secreting tumors in hypertensive patients range from 1.6 to 5%.[11]

Virilizing tumors secreting adrenal androgens are most common in children and the reported prevalence is 20-30% of all adrenocortical tumors.[1,11] Purely feminizing tumors are very rare.

Adrenocortical carcinoma

The most feared diagnosis of AI is ACC [Figure 1]. The incidence of ACC has been reported to range between 0.6 and 2 cases per million per year. Children from southern Brazil have shown unusually high incidence of ACC (3.4-4.2%). ACC is notably more common in women and can be bilateral.[12] The mean survival was estimated to be approximately 18 months and a 5-year overall survival of around 16%.[13] The prevalence of ACC among AI correlates with the size of the mass. ACC accounts for only 2% of tumors up to 4 cm in size. Nonetheless, it accounts for 25% of tumors >6 cm in size.[11] These tumors can be functional or nonfunctional. However, reports suggest that the former accounts for 60% of all ACC.[8]

Adrenal medullary tumors

The inner medulla constitutes for 90% of the adrenal gland. Adrenal medullary tumors include pheochromocytomas and the rare ganglioneuromas, ganglioneuroblastomas and neuroblastomas. The latter are predominantly childhood tumors. Pheochromocytomas are catecholamine producing tumors arising from the chromaffin cells of the adrenal medulla. The estimated incidence is 0.1% and 0.2% in the general and hypertensive population, respectively.[14] The presence of bilateral tumors is commonly associated with multiple endocrine neoplasia type 2 and von Hippel-Lindau syndrome. With approximately 10% of pheochromocytomas being malignant, caution should be practiced in the diagnosis and management.

Trends in management

The management of an incidental adrenal lesion is based on its size, functional status, radiological appearance and patient characteristics.

Radiological evaluation

The size and radiological appearance of an adrenal mass may distinguish benign and malignant lesions. Existing data suggests that tumors <4 cm in size are invariably benign.[4]

Role of computerized tomography

Noncontrast computerized tomography (CT) should be considered the initial investigation of choice [Figure 2]. Benign tumors are characterized by smooth, well-defined borders, diameter less than 4 cm and Houndsfield (HU) attenuation of less than 10 on noncontrast films. For lesions with the above-mentioned characteristics no further imaging is recommended. Patients with masses displaying >10 HU attentuation on noncontrast CT should undergo contrast-enhanced CT for further characterization.[15] Tumor margins, size and enhancement on noncontrast films as compared to contrast films aid in differentiating benign and malignant lesions.

Malignant masses are associated with irregular borders, diameter of more than 4 cm and Houndsfield attenuation

Table 1: Differential diagnosis of adrenal incidentalomas

Adrenal cortical tumors	Adrenal medullary tumors	Miscellaneous
Adenoma	Pheochromocytoma	Myelolipoma
Adrenal cortical carcinoma	Ganglioneuroma	Lipoma
Nodular hyperplasia	Ganglioneuroblastoma	Lymphoma
	Neuroblastoma	Hemangioma
		Neurofibroma
		Cysts
		Hematoma and hemorrhage
		Metastases: Breast, kidney, lung, ovarian, etc.
		Teratoma

of more than 30 units on noncontrast films.[16] Presence of adenopathy favors a malignant disease process.

Studies have shown that with a cut off of 10 HU or less on noncontrast CT, adrenal adenoma can be diagnosed with a sensitivity of 73% and specificity of 96%.[17] Additionally, tumors with less than 30 HU on contrast enhanced CT and more than 50 % washout in 10 minutes delayed films are predictive of adrenal adenomas.[1] The use of contrast enhanced CT increases the sensitivity and specificity of differentiating benign and malignant adrenal masses to 92% and 98%, respectively.

Fat-containing lesions such as myelolipomas can be accurately diagnosed using CT. They are characterized by low attenuation (-30HU) and inhomogeneous appearance on unenhanced CT, in such situations no additional imaging is recommended.[15]

Role of ultrasonography

Abdominal ultrasonography (USG) can detect adrenal masses more than 2 cm in size. However, characterization of the lesion using USG is limited. Transabdominal USG can detect right-sided adrenal lesions in nearly all patients and 69% of left-sided lesions. On the contrary, transgastric USG can detect 98% of left-sided adrenal lesions as compared to only 30% of right-sided lesions.[3,18]

Role of magnetic resonance imaging

Adrenal adenomas present similar signal characteristics as normal adrenals. Adenomas are hypointense to the liver in T1-weighted images and isointense to the liver in T2-weighted images [Figure 2]. Chemical shift magnetic resonance imaging (MRI) has shown increased promise in diagnosing benign adenomas as it reflects the lipid content of tissues. Lipid rich adenomas lose signal intensity on out of phase images.[1] Malignant lesions are known to show higher signal intensity on T2-weighted images.[3]

Pheochromocytomas tend to be hyperintense on T2-weighted images and with gadolinium they display rapid enhancement. This phenomenon is referred to as the light bulb sign. However, the MR light bulb sign is neither sensitive nor specific for the diagnosis of pheochromocytoma. On chemical shift MRI, pheochromocytomas do not show significant signal loss.[3]

Role of adrenal scintigraphy

Adrenal scintigraphy provides both anatomical visualization and an estimate of the functional status of the adrenals. It is noninvasive, and complements imaging data obtained by CT or MRI to further characterize the lesion. In general, masses with discordant or no uptake of tracer should be considered for surgery. Masses with symmetric uptake can be conservatively managed. However, serial imaging is required during follow-up.[3]

Hypersecreting and nonhypersecreting adenomas show radiotracer uptake. However, primary or secondary adrenal malignancies appear as cold nodules.[19,20] Adrenal scintigraphy may be employed in nonhypersecreting masses <4 cm in size.

Adrenal medullary scintigraphy employs the use of radioiodinated guanethidine derivatives such as ^{131}I-MIBG and ^{123}I-MIBG. Both the tracers combined have shown to have increased sensitivity (>95%) and specificity (95%) in identifying pheochromocytomas.[21,22] However, tumors less than 1.5 cm and with extensive necrosis or hemorrhage may yield false negative results due to poor uptake of the tracer. With the possibility of false negative results scintigraphy should be complemented with hormonal evaluation and imaging studies to establish accurate diagnosis. Recent studies have shown that positron emitting tomography (PET) with ^{18}F-fluorodeoxyglucose (^{18}F-FDG PET) has been more successful than MIBG in localizing all sites of adrenal and metastatic pheochromocytoma except bony metastasis.[23] Similarly, the sympathomedullary system can be imaged using somatostatin analogs such as ^{111}

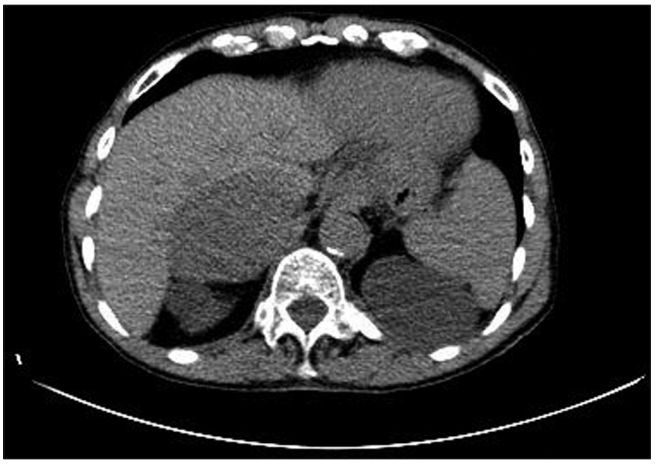

Figure 1: Large right primary adrenal carcinoma

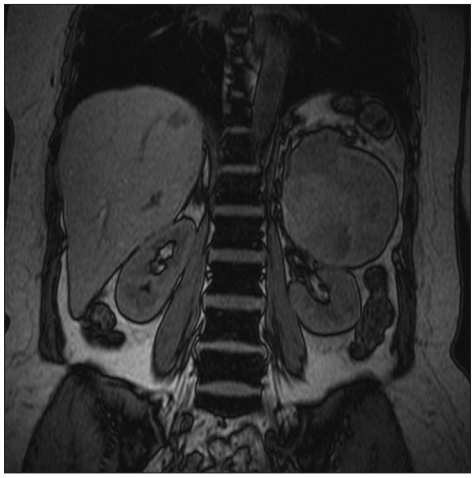

Figure 2: T1 image of large left pheochromocytoma

indium diethyllenetriamine pentaacetic acid D-phenylalanine. Preliminary studies have shown that this imaging modality is more sensitive than MIBG for picking up benign and malignant pheochromocytomas.[24]

Role of fine needle aspiration

Fine needle aspiration (FNA) is only indicated in patients with a heterogeneous adrenal mass displaying an attenuation of more than 20 HU on noncontrast CT and with evidence of metastatic disease. Due to the poor diagnostic ability of cytology, a negative FNA does not completely exclude the possibility of malignancy.[4,25] Currently, there is limited data available to prove the efficacy of FNA and hence it is rarely indicated.

Biochemical evaluation

The functional status of the tumor dictates whether conservative management is feasible or surgery should be considered. There is general consensus that all hypersecretory tumors should be surgically removed.[3]

Pheochromocytoma, aldosteronomas, cortisol secreting tumors, virilizing tumors and adrenal carcinomas are adrenal masses that are commonly evaluated biochemically. Nonetheless, studies have shown myelolipomas to also contain functional elements.[17] Therefore, it may be worthwhile to biochemically evaluate the functional status of all adrenal incidentalomas to avoid surprises.

Pheochromocytomas account for approximately 4% of incidentalomas. The morbidity and possible mortality associated with pheochromocytoma justifies screening with 24-h urine catecholamines and metanephrines. Pheochromocytomas secrete catecholamines episodically but metabolize them continuously. Hence, recent studies suggest that separate measurement of plasma and urine-fractionated free metanephrines (normetanephrine and metanephrine) yield better diagnostic results.[26] Vanillylmandelic acid (VMA) is not recommended for screening of pheochromocytoma due to the lack of sensitivity in the diagnosis.[27] Clonidine suppression test can be employed to distinguish falsely positive increased catecholamine secretion due to sympathetic activation.

Primary aldosteronism can be due to aldosterone producing adenomas (60%) or due to idiopathic hyperaldosteronism (30%). Accurate differentiation is crucial as the former is treated surgically and the latter with medical management. Screening tests include evaluation for hypertension and monitoring potassium levels without dietary salt restriction. Studies have shown that dietary salt restriction can mask hypokalemia in patients with aldosteronomas.[28] In patients with hypertension and/or hypokalemia, measurements of plasma aldosterone (PA) and plasma renin activity (PRA) are indicated. A ratio of PA to PRA of greater than 30 is usually suggestive of aldosterone producing tumor and may mandate additional testing.[29] Adrenal venous sampling may be performed in selected cases when preoperative imaging cannot definitively localize the aldosteronomas. This aids the differentiation of idiopathic hyperaldosteronism from aldosterone producing adenomas.[30]

The diagnosis of subclinical Cushing's should be suspected if two screening tests are abnormal. Screening tests suggested by the Endocrine Society are: Urine-free cortisol (UFC), late night salivary cortisol, and/or low dose dexamethasone suppression test (1 mg) (DST).[25] The criteria for positive DST ranges from 2 to 5 μg/dl. DST is often abnormal in patients with incidentalomas. Additional testing is warranted prior to establishing the diagnosis. Masserini *et al.* studied 104 patients with adrenal incidentalomas and 22 were diagnosed with subclinical hypercorticolism; of these the DST and ACTH levels were abnormal in 86% and 31% had abnormal UFC. The specificity of salivary cortisol testing was reported to be 88%.[31]

Elevated levels of dehydroepiandrostenedione sulfate (DHEA-S) are commonly seen in patients with adrenal carcinoma, congenital adrenal hyperplasia and virilizing tumors. Most adrenal cancers are hormonally active and frequently overproduce adrenal androgens.[17]

Treatment of adrenal incidentalomas

Extensive research has been conducted to define a cost-effective diagnostic and therapeutic protocol to guide physicians in managing incidental adrenal lesions. However, there is little consensus on the optimal management strategy. Published literature to date, describes a wide spectrum of treatment options ranging from excision of all adrenal lesions regardless of the size and functional status to extensive hormonal and radiological evaluation to avoid surgery.

The size and functional status of the adrenal tumor are the two most important factors that should be taken into consideration prior to initiating treatment. The size of the mass is the most important predictor of the risk of malignancy. All adrenal lesions more than 4 cm in size should be removed.[32,33] There is much controversy in surgical removal of smaller lesions (<4 cm). However, many institutions recommend surgery for masses 3-4 cm in size.[34,35] Prevalence of adrenal masses increases with age and suggests vascular rearrangements as a pathognomic mechanism. Therefore, the risk of malignant transformation may be lower in older patients compared to the younger generation. Hence, Staren *et al.* considered age as a criterion for excising adrenal lesions in addition to the size. They recommended adrenalectomy for 3-6 cm adrenal masses in patients younger than 50 years of age, also considering the fact

that surgery is well tolerated in the younger population, lowering the risk of malignancy, prevent subclinical hyperfunction and to possibly avoid long-term follow-up.

Observation and careful surveillance with serial CT scans and biochemical tests are recommended for masses <4 cm in patients older than 50 years and in patients with hormonally inactive masses less than 3 cm in size.[36] Masses with ominous CT characteristics should be removed.

The functional status of the tumor is the second most important criteria dictating the management. All pheochromocytomas and aldosteronomas should be surgically removed; this includes tumors with subclinical hyperfunction. In patients with subclinical Cushing's, the morbidity associated with obesity, hypertension, osteoporosis, diabetes should be considered prior to excising the tumor.[3]

Adrenalectomy performed open or laparoscopically is the treatment of choice for malignant and/or hyperfunctioning tumors. With the advent of laparoscopic adrenalectomy (LA) in 1992, it remains the first choice for both patients and physicians in feasible situations. To our knowledge, there are no prospective, randomized trials evaluating open and LA. To date, several retrospective studies have compared open and LA. Reports suggest that LA is superior in view of excellent operative exposure and visualization, less postoperative pain, shorter hospital stay and convalescent period, and improved cosmetic result.[37-39]

Hyperfunctioning adrenal masses are not a contraindication for LA, hypersecreting tumors including pheochromocytoma have been successfully excised without complications.[40,41] Guerrieri *et al.* compared the anterior, flank lateral and submesocolic approaches during LA and concluded that the approach should be tailored according to the patient's body habitus and lesion characteristics. However, they noted that the anterior and the submesocolic approaches involved shorter operative time.[42] Zografos *et al.* reported their experience of performing LA for patients with tumors more than 8 cm. They concluded that LA for large tumors is feasible and it does not necessitate open conversion. Short-term outcomes were comparable to that of open adrenalectomy.[43] LA, however, has some limitations which include two-dimensional view, unsteady camera, poor ergonomic settings and rigid instruments. On the contrary, robot-assisted adrenalectomy (RAA) offers three-dimensional vision, wristed joint instruments and a steady camera. These features are crucial when considering adrenal sparing surgery in obese patients or where large lesions are present. Short-term outcomes of RAA are comparable to LA.[41] Current literature reports on laparoendoscopic single site (LESS) surgery which has similar operative time to RAA and is a feasible option with minimal technical difficulties encountered.[44,45] Partial adrenalectomy is reported to be a feasible option with low recurrence rates in patients with pheochromocytoma. However, patients require longer follow-up. Open adrenalectomy should be reserved for those tumors with signs of local invasion due to increased risk of tumor fragmentation, incomplete resection and technical difficulties associated with laparoscopic en-bloc tumor retrieval.[46] For recurrent inoperable lesions, tumor ablation would restrain further advancement of disease temporarily.

Surveillance and follow-up

Nonhypersecreting and apparently benign adrenal incidentalomas may be conservatively managed. At the present time there is no consensus on the follow-up imaging and biochemical evaluation for adrenal incidentalomas. The natural course of adrenal tumors and the risk associated with hypersecretion and malignant transformation is not clear at the present time. Some series report hormonal excess may develop in up to 16% of patients and about 11% of tumors increase in size during the follow-up period.[3] Published literature recommends re-evaluation imaging to be performed at intervals ranging from 3 to 12 months after the initial diagnosis.[36,47-50] Considering the radiation exposure, MRI may be preferred over CT.

According to the National Institute of Health (NIH), imaging should be repeated twice within 6-12 month intervals and endocrine evaluation should be performed once every 6 months for 4 consecutive years. For tumors that remain stable during this period, no further follow-up is warranted.[4]

Management of metastatic lesions to the adrenal gland

The adrenal gland is a common site for metastatic lesions. A study on autopsy review of 1000 patients reported metastases on the adrenal gland in 27% of patients[51] [Figure 3]. Adrenal metastases (AM) commonly results due to primary from the lungs, breast, kidney, skin melanomas and gastrointestinal cancers. The mean survival in nonoperated patients is reported to be 6-8

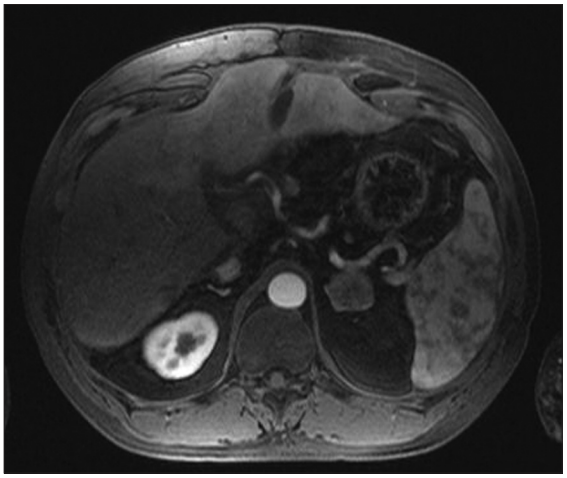

Figure 3: Hepatocellular carcinoma metastatic to left adrenal

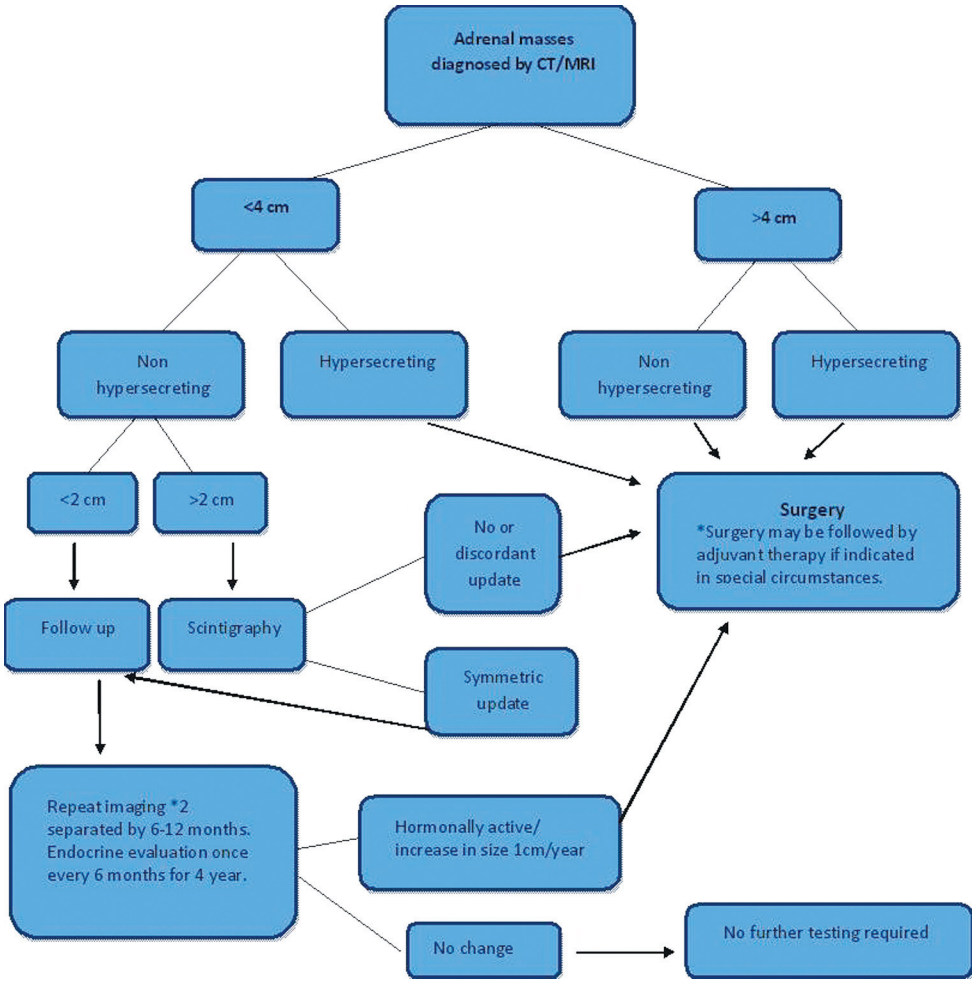

Figure 4: Management algorithm for adrenal incidentalomas

months.[52] On the contrary, long-term survival after surgery for isolated AM is 20- 30 months.[52] With the advent of LA, surgical management of operable AM has gained increasing popularity. However, caution should be practiced to avoid tumor spillage and incomplete resection. Valeri *et al.* reported the outcome of 51 patients with mean follow-up of 38.3 months. One-year survival was 80-90%, the 2-year survival decreased to 50-60% and the 5-year survival was 23%. They suggest LA in all patients with suspected or documented AM. Fine needle aspiration is suggested in those patients with inconclusive diagnosis after complete clinical and laboratory evaluation. Patients with positive or indeterminate diagnosis of AM should be considered for adrenalectomy. LA is comparable to open adrenalectomy based on short and long-term oncological outcomes.[53,54]

CONCLUSIONS

The management of adrenal incidentalomas poses a therapeutic dilemma. All patients should undergo hormonal screening, specific radiological imaging and/or scintigraphy to assess functionality and to avoid unnecessary adrenalectomy. Surgery is recommended for tumors more than 4 cm and/or with evidence of malignancy based on imaging studies. Hypersecreting tumors should be removed. Conservative management for small nonhypersecreting tumors is acceptable. No further testing is warranted for those tumors which have been stable radiologically for over 2 years and biochemically for over 4 years. Fine needle aspiration biopsy is rarely indicated but may be considered in cases with suspicious extra-adrenal malignancy. Figure 4 illustrates a proposed management algorithm for adrenal incidentalomas.

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How to cite this article: Kanagarajah P, Ayyathurai R, Manoharan M, Narayanan G, Kava BR. Current concepts in the management of adrenal incidentalomas. Urol Ann 2012;4:137-44.

Source of Support: Nil, **Conflict of Interest:** None.