Review

DOI: 10.4274/uob.galenos.2022.2022.3.1

Bull Urooncol 2022;21(3):80-86

The Current Approach for Small Adrenal Masses

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Abstract

Adrenal tumors originate from the medulla or cortex of the adrenal gland and may be benign or malignant, functional or non-functional. Adrenal tumors discovered during imaging for non-adrenal indications are called incidentalomas and are more common than non-incidental masses. Most incidentalomas are hormonally inactive and benign. Adrenal masses are approximately 30-35 mm in diameter at the time of diagnosis. While masses less than 4 cm are generally considered to be small masses, they are at lower risk for malignancy than adrenal masses larger than 4 cm. An incidentally detected adrenal mass should be investigated for malignancy and functional activity. Hormonal activity or malignancy of the adrenal mass are indications for surgery. Laparoscopic surgery for adrenal adenomas is the gold standard. Evaluation is important to determine the treatment and follow-up process. Although the frequency of benign small adrenal masses increase with age, even if the mass size is <4 cm in young patients, because of their rarity at this age, a closer follow-up is required. The ideal follow-up schedule for these small masses <4 cm in diameter has not been precisely defined. However, clinical guidelines recommend clinical and hormonal follow-up for at least 4 years, and follow-up imaging [computed tomography (CT), magnetic resonance imaging] 6-12-24 months after the first CT. If the size increase in a followed mass is >0.8 cm/year, surgery is recommended, but the malignancy rate is low in these masses.

Keywords: Adrenal, adrenalectomy, incidentaloma

Introduction

Anatomy and Physiology of the Adrenal Gland

Adrenal glands are organs in the upper part of both kidneys, located at the level of the 11th and 12th ribs, and are approximately 4-5 gr and 0.5-1x4-5x2-3 cm in size. In front of the right adrenal gland is the liver and medially the vena cava. The left adrenal is adjacent to the aorta medially, splenic vein and artery, the body of the pancreas and stomach anteriorly (1,2,3).

The adrenal gland is rich in vascular structure, and during stress, it has 5-6 times the normal blood flow. Blood flow is provided by the superior, median and inferior adrenal arteries. The venous return is directly to the inferior vena cava with a short segment on the right, and to the left renal vein after merging with the inferior phrenic vein on the left (Figure 1). Lymphatic drainage is provided by the paraaortic lymph nodes on the left and the paracaval lymph nodes on the right. Autonomic innervation of the adrenal glands includes preganglionic sympathetic fibers going to the chromaffin cells of the adrenal medulla, while postganglionic fibers originating from the splanchnic ganglia provide innervation of the adrenal cortex (1,2,3,4,5,6). Figure 1 shows the anatomy of the adrenal gland in detail (7).

The adrenal gland consists of the medulla, which functions as a neurocrine organ, and the cortex, which functions as an endocrine organ. The adrenal cortex consists of 3 layers. The zona glomerulosa is the outermost part of the adrenal cortex and is responsible for the production of mineralocorticoids. The zona fasciculata, which is located in the middle layer and forms 75% of the cortex, synthesizes glucocorticoids. The innermost layer is the zona reticularis, which is responsible for androgen synthesis. The adrenal medulla, on the other hand, works as a part of the autonomic nervous system and is responsible for the synthesis and regulation of catelocamines (8).

Adrenal Masses

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Cite this article as: Şenoğlu Y, Balık AY, Ediz E, Yüksel A, Baba D. The Current Approach for Small Adrenal Masses. Bull Urooncol 2022;21(3):80-86

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Received: 09.03.2022 **Accepted:** 28.05.2022

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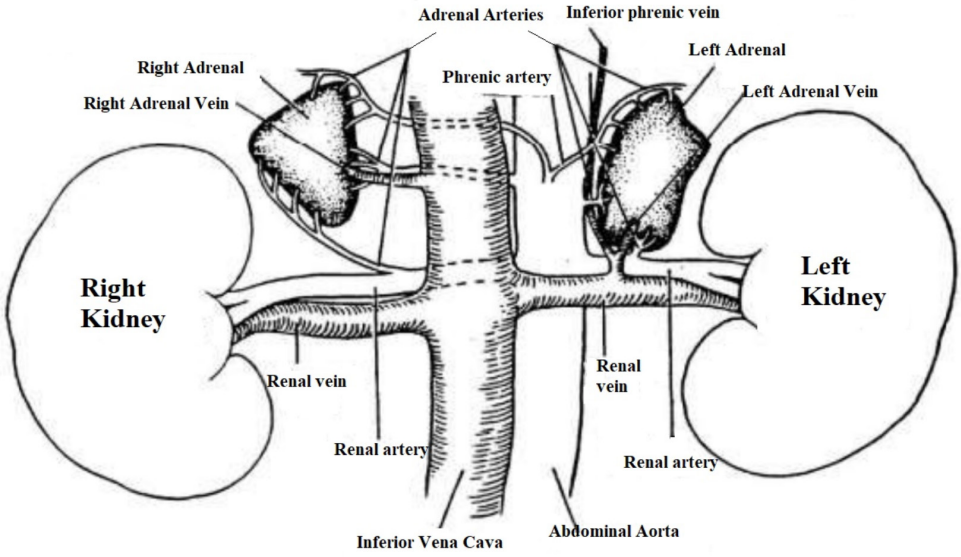

Figure 1. Adrenal gland anatomy (7)

common than non-incidental masses. Most incidentalomas are hormonally inactive and benign. However, in approximately 10% of cases, the adrenal mass may be functional. Cushing's syndrome (CS) is the most common cause of functional tumors originating from the adrenal cortex, while functional tumors originating from the adrenal medulla are most commonly caused by pheochromocytoma. The etiology of adrenal masses was also investigated in the study conducted by the adrenal tumors study group of the Italian Society of Endocrinology, which included 1,004 patients. The etiology and rates of adrenal masses according to this study are summarized in Table 1 (9).

Hormone Evolution

Clinical situations in which the adrenal function is accelerated should be analyzed well.

Cushing Syndrome

CS is the general name of the clinical status that occurs after an increase in glucocorticoids due to endogenous or exogenous causes. The most common cause is exogenous steroid intake. Endogenous causes are classified as adrenocorticotropic hormone (ACTH)-dependent (caused by pituitary or ectopic tumor) (80%) and ACTH-independent (caused by adrenal gland) (20%) (10,11).

Tests can be used to screen patients for hypercortisolemia. These tests are; Dexamethasone suppression test, salivary cortisol level at midnight (repeated two or three times), free cortisol level in 24-hour urine. If hypercortisolemia is detected by these tests, ACTH determination should be made. Adrenal masses that secrete cortisol are ACTH dependent. The first choice among these tests is the dexamethasone suppression test. Although there is no consensus in the literature on the amount of dexamethasone for this test (1 mg, 2 mg for 2 days, 3 mg or 8 mg), the mostly recommended approach is to determine the cortisol in the blood measured at 08:00 the next morning after an oral 1 mg dexamethasone tablet at 23:00. As a general opinion, for subclinical CS, the cortisol value measured after the test has been reported as 5 mcg/dL.

For cortisol values below 1.8 mcg/dL after dexamethasone, ACTH-independent autonomic glucocorticoid-secreting pathologies should be excluded. Patients with a cortisol level of 5 mcg/dL and above in the dexamethasone suppression test should be considered as subclinical CS (or CS if clinical findings are evident). Intermediate values should be considered on a patient basis and the above-mentioned tests should be used for further examination for the diagnosis of subclinical CS (12,13,14,15).

Primary Hyperaldosteronism (Conn Syndrome)

The increase in aldosterone levels due to the involvement of the glomerulosa layer of the adrenal cortex is responsible for the formation of a clinic such as hypertension, hypokalemia, hypernatremia, metabolic alkalosis and polyuria. Its prevalence in the hypertensive patient population has recently been reported to increase to 5-16%. The most common cause is bilateral adrenal hyperplasia. Other causes include aldosteronomas, adrenal carcinomas, and glucocorticoid-regulated hyperaldosteronism (16,17). Adrenal vein sampling is currently performed to confirm that the present mass is the pathology causing hyperaldosteronism.

In the differential diagnosis of an incidental adrenal mass, plasma potassium, renin and aldosterone levels should be checked for primary hyperaldosteronism. As a screening test, the ratio of serum aldosterone level (ng/dL)/plasma renin activity (ng/mL/hour) is used. If this ratio is above 20, it is necessary to proceed to confirmatory tests and subtyping tests. Since the renin-angiotensin-aldosterone system can also be affected by postural changes, some rules must be followed while performing the

test. The patient should be called for sampling in the morning hungry, at least half an hour must have passed after getting out of bed, and sampling should be done after the patient has been sitting for at least 15 minutes. Some drugs and renal dysfunction may affect the result of the test. For this reason, antihypertensive treatments used by the patient should also be reviewed and discontinued before the procedure (14,18).

Pheochromocytoma

Pheochromocytoma is a tumor of the adrenal medulla with catecholamine overproduction. About 1-2 in 100,000 people a year are diagnosed with pheochromocytoma. In most studies, it has been stated that pheochromocytomas constitute 4-7% of incidentalomas (19,20). Pheochromocytomas can be seen as a part of sporadic or hereditary syndrome [multiple endocrine neoplasia type 2 (MEN-2A or 2B), neurofibromatosis type 1 (NF-1), Von Hippel-Lindau syndrome, Sturge-Weber syndrome and Von Recklinghausen disease etc.] (21). Tumors are predominantly in the adrenal medulla. Also have a malignant potential of 10% and are seen bilaterally in 10% of cases (22).

Pheochromocytoma is a pathology that must be kept in mind when evaluating an adrenal mass. Pheochromocytoma should be screened whether the patient has hypertension or not. The most appropriate screening test is the evaluation of fractionated metanephrines in a 24-hour urine sample. For an ideal test, patients should restrict their fluid and food intake after midnight. In addition, drugs such as levodopa, labetolol, tricyclic antidepressants, sympathomimetics, severe infection, acute cardiovascular events may alter fractionated metanephrine excretion and cause misdiagnosis. In order to exclude the diagnosis of pheochromocytoma as a result of the test, urine fractionated metanephrines should be found to be normal. For the diagnosis of pheochromocytoma, the fractionated metanephrine levels were required to be 3-4 times higher than the upper limit of the reference range of the test. In addition, for the differential diagnosis of pheochromocytoma, plasma catecholamine level, plasma free metanephrine level, and plasma normetanephrine level should also be measured (23,24).

Other

Tumors that secrete sex hormone are symptomatic in the early period and are less likely to be seen incidentally, as they manifest themselves by virilization or feminization. The most common adrenal lesion with sex hormone secretion is adrenal carcinoma, and it is usually accompanied by excessive cortisol secretion. For this pathology, dehydroepiandrosterone sulfate (DHEA-S) level, testosterone and estradiol are measured. An increase in DHEA-S suggests the presence of adrenal androgens and shows a level proportional to the size of the adrenal mass. DHEA-S is important for the differentiation of benign and malignant. It reaches very high values in adrenal carcinoma. For differential diagnosis, serum 17-OH progesterone level and corticotropin stimulation test are performed. About 50% of the adrenal lesions that secrete sex hormone are benign. For this reason, routine screening testing is not recommended (25,26).

Radiological Imaging in Small Adrenal Masses

Many methods can be used for imaging adrenal masses. Table 2 summarizes the criteria that can be used to differentiate benign and malignant lesions in adrenal masses radiologically. Today, in the light of technological developments, there has been an increase in the diagnosis of adrenal masses that are small in size with radiological imaging methods (27).

Ultrasonography

Ultrasonography (USG) is frequently used in the evaluation of large sized masses and can detect up to 65% of small adrenal masses (<3 cm) (28). Right adrenal lesions are seen more frequently with ultrasonography in the diagnosis of incidentaloma. Ultrasonographic evaluation of adrenal masses is more difficult on the left side due to the anatomical position of the organs (29).

Computed Tomography

Computed tomography (CT) is the first choice for the detection and classification of especially small adrenal masses. However, computed tomography does not provide the opportunity to differentiate about the function of the adrenal mass.

On unenhanced CT, adrenal masses with ≤10 Hounsfield units are usually diagnosed as adrenal adenoma. In recent years, washout has been used routinely to differentiate lipid-poor adenomas from other adrenal masses (30).

Magnetic Resonance Imaging

It is important to distinguish adrenal masses as adenoma and non-adenoma. Adrenal adenomas usually give an equal or lower signal than the liver on T2-weighted images. Adrenocortical carcinomas are hyperintense compared to the liver in T2 on magnetic resonance imaging (MRI), they do not lose signal on MRI (31). Metastases do not lose signal on MRI and are more hyperintense on T2 compared to the liver (32). Pheochromocytomas appear hypointense on T1-weighted images and characteristically bright on T2-weighted images (33).

Table 1. Adrenal masses, etiology and percentages

Tumor type	Percent (%)
Hormonally inactive tumors	74
Hormonally active tumors	
Cortisol secreting (Cushing)	9.2
Pheochromocytoma	4.2
Aldosteronoma (Conn)	1.5
Adrenal carcinoma	4.0
Other adrenal tumors	
Myelolipoma	3
Cysts (cyst, pseudocyst)	1.9
Ganglioneuromas	1.5
Adrenal metastases	0.7
Other (teratoma, hematoma, hamartoma, neurofibroma, amyloid, granuloma)	

Positron Emission Tomography Pet (18F-Fluorodeoxyglucose)

While metabolic activity is increased in most malignant adrenal masses, no activity is observed in benign masses. It may be useful in small adrenal metastatic mass or adrenocortical carcinoma (34).

Biopsy in Small Adrenal Masses

Histologically, it is not reliable enough to distinguish adenomas from carcinomas. The place of adrenal biopsy is limited due to its complications and risks (bleeding, pneumothorax, hemothorax, adjacent organ injury, pancreatitis, etc.). With modern imaging and clinical characters, a nearly complete diagnosis can be achieved (35). In cases where the diagnosis of small adrenal masses cannot be made clearly or in the presence of suspected metastasis, USG or CT-guided biopsy is helpful (36).

Treatment in Small Adrenal Mass

Indication criteria for adrenal mass surgery are mainly the size of the mass, hormonal activity of the mass and radiological features.

Mass Size

According to the American National Health Organization, it is recommended that masses >6 cm in size be considered malignant and surgically removed until proven otherwise. Between 4-6 cm in size, the decision should be made according to the hormonal status of the patient, clinical findings and radiological appearance of the mass (37). In a study, no adrenocortical cancer cases were found in masses <4 cm. Therefore, it is stated that a threshold value of 4 cm for excision may be effective in reducing surgery for benign tumors since it has a high sensitivity of 93% despite low specificity in identifying primary malignant tumors (38). Despite this, it is stated that asymptomatic myelolipoma and simple cysts may not require surgery even if the diameter is larger than 4 cm (39).

Although the frequency of benign small adrenal masses increases with age, even if the mass size is <4 cm in young patients, because of their rarity at this age, a closer follow-up is required. If the size increase in a followed mass is >0.8 cm/year, surgery is recommended, but the malignancy rate is low in these masses (40).

In summary, surgical recommendations based on tumor size are derived from non-standardized studies on the duration of follow-up or estimating the risk of carcinoma. For this reason, a threshold value of 4 cm is used when surgical removal of the mass is required, but surgical treatment may be preferred for masses larger than 6 cm in clinical approaches. It is generally accepted that masses smaller than 4 cm should also be followed. The threshold value of 4 cm is more important in making the decision to follow the masses below this size. In patients with a tumor between 4 and 6 cm, the removal of the mass should not only be based on size, but also other criteria should be taken into consideration. The literature on adrenal incidentaloma has increased over the past few years. Unfortunately, the lack of controlled studies makes it difficult to formulate diagnosis and treatment strategies. More studies are needed on this subject (28,37,41).

Hormonal Activity

Surgical treatment is recommended regardless of the size of hormone-producing functional masses, including small adrenal masses. Surgical resection is recommended in patients with clinically asymptomatic aldosteronoma and pheochromocytoma because of the possibility of life-threatening complications (28,42,43). In the presence of a clinically symptomless condition described as preclinical CS, especially in young patients. Since it has been shown that metabolic conditions such as hypertension, obesity, diabetes and osteoporosis can improve after surgery, surgical treatment is also recommended in this clinical situation (44,45).

Radiological Appearance

Important criteria for radiologically benign-malignant distinction are given in Table 2. Among these criteria, chemical shift MRI has the highest specificity and sensitivity in the differentiation

Table 2. Criteria that can be used to differentiate benign and malignant lesions radiologically (24)

Criteria	Malign	Bening
Size	>4 cm	<4 cm
Homogeneity	Heterogeneous	Homogeneous
Growth rate	Fast	Slow
Contrast uptake	Different rates of uptake, slow clearing	Fast uptake, fast clearing
MRI signal on T2	High	Low
Signal loss out of phase on MRI	<30%	>30%
Shape-border	Thick/Irregular	Round/Regular
Adrenal/Splenic ratio	>70%	<70%
Density in CT	>10 HU	<10 HU (lipid-rich) >10 HU (lipid-poor)
Lipid ratio	Low	High (except lipid-poor ones)
Absolut washout	<60%	>60%
Relative washout	<40%	>40%

MRI: Magnetic resonance imaging, CT: Computed tomography, HU: Hounsfield units

of benign and malignant. In general, in radiological evaluations, surgical resection is recommended for rapidly growing masses, heterogeneous or irregularly circumscribed, containing necrotic or calcified areas, and invading adjacent structures (46).

Surgical indications can be summarized as follows (47,48):

- >4 cm masses
- Isolated adrenal metastases
- Masses that grow ≥1 cm in follow-up
- Functional adrenal masses (excessive cortisol secretion, pheochromocytoma, excessive aldosterone secretion)
- Giant or symptomatic myelolipoma
- Presence of radiological findings with suspicion of malignancy.

Pre-surgery Patient Preparation

Hormonally active adrenal masses can cause two main serious conditions such as acute adrenal insufficiency and hypertension crisis. In CS, in the preoperative period, the patient's hyperglycemia and electrolyte imbalance should be regulated and the operation should be performed under steroid support. In the postoperative period, the steroid dose should be decreased gradually and support should be continued for the recovery of the hypothalamo-pituitary-adrenal axis (49).

Preoperative preparation is important for pheochromocytoma. A complete cardiac examination, including electrocardiography and echocardiography, in the preoperative period is important to evaluate the end-organ damage that may be caused by hypertension. In order to provide hemodynamics and blood glucose regulation, preoperative sympatholytic therapy with α-adrenergic blockers should be started at least 2 weeks before the surgery and continued until the day of surgery. The most commonly used of this group is phenoxybenzamine, a long-acting alpha-blocker. Despite all the preparations, it was also determined that there were hypertension crises during the removal of the tumor (50).

Surgical Methods in Small Adrenal Masses

Large left adrenal tumor was totally removed by Knowsley-Thornton in 1889 in a 36-year-old female patient with hirsutism. In 1992, the first successful transperitoneal laparoscopic adrenalectomy was performed by Gagner (2,51).

When laparoscopic adrenalectomy is compared with open surgery; it offers less pain, shorter hospital stay, less blood loss and faster recovery. Currently, the laparoscopic approach is used in most adrenal masses (52). In patients with known or suspected adrenal carcinoma, the laparoscopic approach is generally preferred if the adrenal mass is <10 cm in diameter and no local invasion is apparent. Apart from this, open adrenalectomy is recommended for all large (>10 cm) adrenal masses (53,54). The reason why robotic adrenalectomy is especially preferred today is that the right adrenal vein is shorter and the limitation of movement due to the location of the adrenal tissue under the liver is eliminated.

Open Adrenalectomy

Open surgery can be performed with a retroperitoneal or transperitoneal approach. Frequently, the transperitoneal subcostal anterior approach provides better exploration of large tumors and better access to the retroperitoneum and great vessels. In obese patients, the lateral extraperitoneal approach is generally preferred. The posterior retroperitoneal approach may be preferred in patients who are prone to wound complications due to a history of cardiopulmonary disease or CS, have undergone previous abdominal surgery and are at high risk of abdominal adhesions. The positive aspects of the retroperitoneal approach are less ileus and short hospitalization, but it should be known that the retroperitoneal approach is difficult, especially in obese patients. It is not suitable for masses >6 cm because the working area is small (42).

Laparoscopic Adrenalectomy

The most widely used method in the world is laparoscopic transabdominal adrenalectomy. It is performed transperitoneally or retroperitoneally, and there is no difference between these methods in terms of operative parameters. For this reason, the choice of the surgeon and the condition of the patient are important when deciding between the two methods. Especially in the presence of large and irregular tumor, un-block removal of the tumor and surrounding adipose tissue is important, as there is a possibility of malignancy (55).

In general, if a patient is suitable for anesthesia for open surgery, laparoscopic surgery can also be performed for the same patient. Laparoscopic adrenalectomy can be considered the treatment of choice for all benign adrenal tumors from 12 cm to 14 cm in size. It remains unclear whether laparoscopic resection of masses ≥8-10 cm or potentially malignant tumors is appropriate due to technical difficulties and concern for local recurrence. However, large tumors suspected to be primary malignancies based on imaging features should be approached with an open technique. In addition, it is better to avoid the laparoscopic technique in obese patients or patients with Cushing's disease until the surgeon has sufficient experience in laparoscopic adrenalectomy. Irrespective of tumor size, morbidity, mortality, and hospital stay are similar to open surgery, but experience is required in both laparoscopic and adrenal surgery. Therefore, indications and contraindications for laparoscopic adrenalectomy are closely related to the skill and experience of the surgeon (56,57,58).

Transperitoneal Approach

Although it is often applied with the lateral approach, it can also be preferred with the anterior approach. The advantage of the lateral position is that it offers a larger working area due to the lowering of the intestines.

Retroperitoneal Approach

This method is applied in the full lateral position. It is preferred in unilateral and relatively small adrenal masses due to its smaller working area compared to the transperitoneal approach (<4-5 cm). It is not preferred for symptomatic pheochromocytoma (59).

Partial Adrenalectomy

Partial adrenalectomy can be considered as an alternative to complete adrenalectomy for small or possibly benign adrenal lesions and is generally preferred for bilateral small lesions (60). Although there is no specific consensus, it is considered

reasonable to perform partial adrenalectomy to preserve the adrenal gland in lesions <3 cm located anterior or lateral to the adrenal gland (61).

Robotic Adrenalectomy

This method, which is performed with the help of a robot, can be applied transperitoneally or retroperitoneally. Especially robotic surgery is more suitable in retroperitoneal adrenalectomy, since the mobility of the tools to be used in the retroperitoneal area is more limited in other methods (62).

Monitoring

Periodic follow-up is recommended in small, hormonally inactive adrenal masses <4 cm in diameter, if there is no radiological suspicion of malignancy. The ideal follow-up schedule for these small masses <4 cm in diameter has not been precisely defined. However, clinical guidelines recommend clinical and hormonal follow-up for at least 4 years, and follow-up imaging (CT, MRI) 6-12-24 months after the first CT. In order to make radiological comparison, the same method should be used in the follow-up. At the end of 4 years, there is no data on the necessity of continuing follow-up in cases where there is no progress in hormonal and clinical follow-up performed annually and there is no increase in lesion size radiologically (28,63).

Conclusion

Adrenal masses are approximately 30-35 mm in diameter at the time of diagnosis. While masses less than 4 cm are generally considered to be small masses, they are at lower risk for malignancy than adrenal masses larger than 4 cm. An incidentally detected adrenal mass should be investigated for malignancy and functional activity. These evaluations are important to determine the treatment and follow-up process.

Acknowledgements

Publication: The results of the study were not published in full or in part in form of abstracts.

Contribution: There is not any contributors who may not be listed as authors.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Y.Ş., Design: Y.Ş., Supervision: Y.Ş., A.Y., D.B., Data Collection-Processing: A.Y.B., E.E., Analysis-Interpretation: A.Y.B., Writing: Y.Ş., Critical Review: E.E., A.Y., D.B.

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