Management of Adrenal Masses

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Abstract An adrenal mass can be either symptomatic or asymptomatic in the form of adrenal incidentalomas (AIs) in up to 8 % in autopsy and 4 % in imaging series. Once a diagnosis of adrenal mass is made, we need to differentiate whether it is functioning or nonfunctioning, benign, or malignant. In this article, we provide a literature review of the diagnostic workup including biochemical evaluation and imaging characteristics of the different pathologies. We also discuss the surgical strategies with laparoscopy as the mainstay with partial adrenalectomy in select cases and adrenalectomy in large masses. Follow-up protocol of AIs and adrenocortical carcinoma is also discussed.

Keywords Adenoma · Adrenocortical · Pheochromocytoma · Adrenal cancer · Adrenal incidentaloma

Introduction

The prevalence of adrenal mass is fairly common in general populace with the autopsy series of 3 to 5 % [1] and 0.5 to 10 % on imaging with contrast-enhanced computed tomography (CECT) of the abdomen [2]. The prevalence of adrenal

adenomas increases with increasing age with a probability of 0.2 % in third decade to 7 % in eighth decade.

Majority of these lesions when detected incidentally are benign nonfunctioning adrenal adenomas [3] but may also be functional and secreting tumors [4]. Hence, our aim during evaluation of these masses would be to differentiate benign from malignant and functioning from nonfunctioning. A comprehensive evaluation of the mass helps the clinician in arriving at a decision with respect to the treatment. The benign so-called leave-alone masses like nonfunctioning adenomas, myelolipomas, cysts, pseudocysts, or unclassified lesions with long-term stability could just be observed, while the functioning and malignant tumors require in majority of cases surgical resection and in some cases medical therapy. Also, distinguishing the masses helps in preparation and perioperative management according to the type of functioning lesion and later in the follow-up.

Clinical Examination

One of the first steps in the evaluation of the adrenal mass like any other case begins with a diligent history and physical examination with a focus on symptoms and signs that will be due to hyperfunctioning or malignant nature of the mass. These signs and symptoms are quite well described in the literature [5].

Biochemical Evaluation

Cushing's Syndrome Overnight low-dose dexamethasone suppression test (LDDST) is used as a screening test with a sensitivity of 73–100 and 90 %, respectively [6]. Values >5 µg/dl (138 nmol/l) are diagnostic. False positives occur

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with medications that accelerate hepatic metabolism of dexamethasone like anticonvulsants and with noncompliance to drug regimen. To decrease this false positivity, a high-dose DST can be used in which a higher dose (2, 3, or 8 mg) is used. Confirmatory test can be done using serum corticotropin, cortisol in a blood and 24-h urine specimen, and midnight salivary measurement of cortisol [4].

Phaeochromocytoma (PHEO) Fractionated metanephrine and catecholamine in 24-h urinary specimen are recommended with a high sensitivity and specificity (91–96 %). Fractionated plasma-free metanephrine is useful with a high sensitivity (96–100 %), albeit with a reduced specificity (85–89 %) and in elderly further reducing to 77 % [7–10]. This can be used for confirmatory testing. False positives are seen in patients in whom there can be an increased production of endogenous catecholamines like prolonged illness and medications like tricyclic antidepressant.

Primary Aldosteronism Measurement of serum potassium is not a reasonable screening test for patient with primary aldosteronism in lieu of a normal level. Morning ambulatory plasma aldosterone concentration to plasma renin activity (PRA) is an appropriate investigation. A plasma aldosterone concentration and plasma renin activity ratio of ≥ 20 and a plasma aldosterone concentration of ≥ 15 ng/dl are considered positive results. Patients on potassium-sparing diuretics need to discontinue the drug at least 4 weeks prior to testing [6, 11, 12]. Confirmatory tests include aldosterone suppression testing with either a saline infusion test or 24-h urinary aldosterone excretion test while the patient maintains a high-sodium diet [13]. Adrenal venous sampling should be considered in patients with bilateral adrenal hyperplasia to confirm that the mass is the cause for hyper-aldosteronism.

Other Biochemical Evaluation Sex hormone evaluation is to be done in patients with clinical manifestations of virilization and hirsutism. Cosyntropin stimulation testing with the measurement of cortisol precursors (e.g., 17-hydroxyprogesterone) is reserved for patients in whom the diagnosis is suspected on the basis of clinical manifestations (e.g., hyperandrogenism) or the presence of bilateral adrenal masses [4].

Imaging

Various imaging modalities are being used for adrenal pathologies. Of these, CECT of the abdomen and pelvis is the most commonly performed followed by magnetic resonance imaging (MRI), and positron emission tomography CT (PET-CT) is usually reserved for patients with possible extra-adrenal malignancy. Metaiodobenzyl-guanidine (MIBG) and less commonly octreotide scintigraphy may be used to identify

pheochromocytomas selectively in patient with a high probability of disease like family history, associated hereditary disorder, and extra-adrenal tumors.

CECT The adrenal CT imaging protocol consists of a multi-phase study including an unenhanced scan followed by a 1-min delayed enhanced scan and a 15-min delayed de enhanced scan. The three phases together are used for calculating absolute percentage washout (APW) and/or relative percentage washout (RPW) in order to differentiate lipid-poor adenomas from primary carcinoma and metastases.

The APW is calculated using the formula:

$$\text{APW} = \frac{(\text{enhanced HU}) - (15\text{min delayed HU})}{(\text{enhanced HU}) - (\text{unenhanced HU})} \times 100 \%$$

An APW value of greater than 60 % is diagnostic of an adenoma. In the absence of an unenhanced phase, a RPW is calculated as follows:

$$\text{RPW} = \frac{(\text{enhanced HU}) - (15\text{min delayed HU})}{(\text{enhanced HU})} \times 100 \%$$

A RPW value greater than 40 % is diagnostic of an adenoma [14]. Adenomas are one of the most common adrenal lesions characterized by intracellular lipid which help in differentiating them from malignant masses. Lipid-rich adenomas usually have a Hounsfield unit (HU) less than 10 with 71 % sensitivity and 98 % specificity [15, 16]. Washout analyses have been found to be accurate in many studies [17–19].

Pheochromocytomas have a variable appearance on CECT with small lesions being homogenous while the larger ones being heterogeneous with areas of necrosis and hemorrhage [20].

Adrenocortical carcinomas (ACC) are usually large (>6 cm) heterogeneously enhancing with areas of central necrosis and hemorrhage and calcifications in 30 % [21]. They may also be invading locally with venous extension being common [22]. Adrenocortical carcinoma generally has APW and RPW values of less than 60 and 40 %, respectively, compatible with nonadenomas [23]. Metastases to adrenal are non-specific with heterogeneous densities, necrosis, and irregular margins in the larger masses, while in smaller masses, they are more homogenous with smooth margin [24]. Quite often, they are bilateral in location.

MRI An adenoma appears dark on out of phase images while using spleen as reference. They can be differentiated from metastasis with a sensitivity of 81–100 % and specificity of 94–100 % [25, 26]. Of adrenal adenomas, 20–30 % are lipid-poor; thus, they cannot be diagnosed with CT or MRI.

PHEOs on MRI classically appear as markedly hyperintense on T2 weighted (T2W) images, although some of the recent series have found them to be moderately hyperintense

or even hypointense [26, 27]. On MRI, ACC appear heterogeneously iso to slightly hypointense on T1W but hyperintense with hemorrhage. On T2W, they are heterogeneously hyperintense. The advantage of MRI over CT is for patients in whom iodinated contrast cannot be used due to allergy or renal impairment or young/pregnant patients in whom radiation is a concern.

PET-CT Malignant masses have increased metabolic activity and hence being avid to glucose form the basis of PET in radiotracer malignant masses. Comparison with the background liver activity and the qualitative visual assessment of uptake as well as quantitative assessment using standard uptake values (SUV) helps to establish the nature of lesion. Most of the malignant adrenal masses show increased activity while the benign ones do not, with the sensitivity for this being 93–100 % [28–31].

MIBG This nuclear medicine modality is used to localize pheochromocytoma with a sensitivity of 95–100 % and specificity of 100 % [32]. It is of particular use in patients with in whom biochemical evaluation is positive but the imaging with CT/MRI is negative [33]. It is also used in detection of metastasis in patients with pheochromocytoma. In cases with biochemical evidence of pheochromocytoma but negative MIBG, octerotide scanning can be used as an alternative. Iodine-131 MIBG therapy may be used for systemic treatment of select patients with metastatic pheochromocytoma [34].

Percutaneous Biopsy

Biopsy for adrenal lesions is done in an indeterminate adrenal mass with a known primary. Ultrasonography-guided biopsy is feasible but CT guided is more commonly done as it is safe with low complication rate and accurate [35]. It is done with ipsilateral decubitus position as this compresses the lung and reduces the movements thereby decreasing chances of pneumothorax. A caudal to cephalad approach is used and on the right side transhepatic approach may be needed.

In a suspected ACC, biopsy is not advocated in surgical candidates in lieu of risk of tumor spillage and making the disease incurable [36]. Also suspected pheochromocytoma should be ruled out prior to biopsy as it may precipitate adrenergic crisis [37]. The complication rate for biopsy is 2.8 % [35] with possible complications of adrenal hematoma, abdominal pain, hematuria, pancreatitis, pneumothorax, and formation of an adrenal abscess.

Indications for Surgery Presence of symptoms or biochemically functioning tumors is an indication for surgical intervention in adrenal masses. In asymptomatic masses, various clinical, radiologic, biochemical, and histologic criteria help in

distinguishing malignant from benign lesions thus determining which all can be observed and which are to be excised [38, 39]. Before recommending surgery, one should consider the patient age, comorbidities, and clinical judgment [40].

Functioning Tumor Biochemically active masses should be considered for surgical removal. Clinically silent lesions are an area of controversy. Pheochromocytomas that are clinically silent but biochemically active should be removed due to the potential life-threatening complications. Another area of contention is the subclinical Cushing's syndrome, although off late few RCTs have demonstrated improvement in clinical and metabolic parameters like diabetes mellitus, hypertension, obesity, and osteoporosis after removal of the adrenal mass in such patients [41, 42]. But to generalize it and recommend universal excision at present are not advisable. Surgery should be advised in young individuals and those with refractory or worsening disease due to cortisol excess [40]. Medical treatment also can be advised in poor surgical patients of primary hyperaldosteronism.

Size In 2002, NIH state-of-the-science statement on management of the clinically inapparent adrenal mass recommended resection of masses more than 6 cm [43]. Recommended size has varied from 2.5 to 6 cm [44–47]. This in effect reflects the limitation of taking size as a criterion for resection. Various studies have reported a low yield for malignant tumors when adrenalectomy is done with size as an indication [46, 48]. One of the reasons is a higher prevalence of benign adrenal masses with larger size [49]. Another limitation is the presence of malignant tumors sometimes measuring <2.5 cm at the time of diagnosis and in some studies in size <5 cm [46, 48]. Ballian et al. did not find any ACC in lesion size less than 4 cm and suggest that a 4-cm threshold for resection would identify primary malignant tumors and decrease the surgery for benign tumors with a high sensitivity of 93 % albeit a low specificity 42 % in predicting malignancy [47, 49].

Laparoscopic adrenalectomy (LA) has become the gold standard for the management for adrenal masses since it was first reported by Gagner et al. in 1992. It has all the advantages of minimal access surgery including cosmesis, decreased post-operative pain, perioperative complications, hospital stay, faster recovery, cost-effectiveness, and more effective use of health care expenditure [50–53]. Various approaches such as transperitoneal (anterior/lateral) and retroperitoneal (lateral/dorsal) have been described with each having its own pros and cons.

LA for Large Masses LA in large mass is the concern for malignancy. We and others have found that LA is safe and feasible in large masses provided the surgeon has adequate experience and a low threshold for conversion. Although there is no size cutoff, masses more than 12 cm have greater

technical difficulty, longer operating time, increased blood loss, more complications, and potential for malignancy with adjacent organ involvement. Terminal hand assistance can be attempted for dissection of such large masses for the haptic feel that is lacking in LA [54].

LA in ACC The concern with LA for suspected ACC has been possible macroscopic incomplete resection, tumor capsule violation, conversion from laparoscopic to open surgery, and microscopic periadrenal fat invasion on final pathology. All the above probably contribute to the increased recurrence locally, at the port site, and peritoneal carcinomatosis. 2015 National Comprehensive Cancer Network (NCCN) guidelines recommend open adrenalectomy instead of LA in suspected cases of ACC [45, 55, 56]. In a debate on OA versus LA in ACC at the third International Adrenal Cancer Symposium, the debater suggested that LA can be considered if it is being performed at a referral center with sufficient experience in such case and also the mass can be resected without rupturing [57]. If LA is attempted, one should have a very low threshold for conversion to open surgery and adherence to strict oncologic principles. Also the use of flexible ultrasound probes and use of wound protector evacuation of the pneumoperitoneum through the port and peritoneal wound closure have been suggested [58].

Perioperative adequate preparation forms the cornerstone especially in pheochromocytoma. In PHEOs, alpha blockade and as required beta blockade are done prior to surgery for adequate duration. It has been found in various series and by us also that in spite of the preparation, fluctuations are seen during handling of tumor. For Cushing's syndrome, adequate hormone replacement perioperatively is to be continued as required in the postoperative period particularly in bilateral adrenalectomies in refractory cases [59].

LA is safe and effective in simultaneous cases particularly in refractory Cushing's syndrome [60]. It can also be done in cases of bilateral PHEOs in patients with multiple endocrine neoplasia syndromes (MEN).

A meta-analysis review comparing robotic adrenalectomy with laparoscopic adrenalectomy found that the robotic approach was safe and effective. The conversion rate and operating time are similar in RA versus LA. A transperitoneal approach was used in both approaches but LA had a significantly longer hospital stay and a higher blood loss [61].

Conventional laparoscopy and LESS are the most commonly utilized technique, whereas mini-laparoscopy and robotics have been slower in growth.

Partial Adrenalectomy (PA) In the last two decades, there has been an increasing interest in partial adrenalectomy [62]. Adrenal insufficiency following bilateral adrenalectomy results in lifelong risk of morbidity from the Addisonian crisis (35 %). It decreases the quality of life and has a mortality rate

of 3 % [63–66]. As of now, the indications for PA are hereditary adrenal tumors, bilateral tumors, and tumors in a solitary adrenal gland. Bratslavsky et al. in their review estimated the incidence of bilaterality in adrenal tumors between 4.25 and 80 %. The hereditary PHEOs (MEN syndrome and VHL) were bilateral in up to 80 %, while the nonhereditary PHEOs (pediatric and incidentalomas) were bilateral in 25 %. Aldosterone-producing adenomas were bilateral in about 4 % cases of PA. They also calculated the probability of lifetime risk of adrenal involvement/damage in the general population from all various diseases to be around 0.98 % [67]. Pediatric patients bear a high risk for Addisonian crisis in view of their longer life expectancy [68].

PA is a safe and feasible procedure by laparoscopy [69–72]. Some of the centers prefer subtotal adrenalectomy. The prerequisite for PA is to leave a segment of well-vascularized cortex after excising the tumor [73–75]. This can be done using intraoperative ultrasound and ultrasonic shears (Harmonic scalpel; Ethicon, Cincinnati, OH). The intraoperative ultrasound aids the surgeon in defining the plane between normal tissue and the mass allowing maximum preservation of the normal adrenal tissue and its vascular supply.

The concerns with PA include the risk of recurrence with cortical sparing adrenalectomy of 21–60 % [73] leading to lifelong clinical and biochemical surveillance to detect the recurrence. In aldosterone-producing adenoma (APA), it has been found that although most of the tumors are small, solitary, and located in the periphery, there may be microadenomas or nodules that cannot be identified by CT [76]. This can result in an increased risk of recurrence in unilateral cases (5.3–27 %) [77]. Repeat PA is also feasible using minimal access techniques like laparoscopy and robotic approach [78]. Recently, robotic partial adrenalectomy with intraoperative indocyanine green dye with near infrared fluorescence imaging (ICG-NIRF) is safe and feasible. The addition of ICG-NIRF may help in mass identification and excision and promote the use adrenal-sparing surgery [79].

ACC if amenable to surgery should undergo the same. Transarterial embolization is used with a palliative intent in patients who are poor surgical candidates or have unresectable tumor [80]. It provides pain relief, hormone suppression and decrease in tumor bulk, and vascularity in surgical cases [81]. Similarly transarterial embolization and percutaneous thermal ablation have been used in treatment of pheochromocytoma in poor surgical risk patients. Alpha blockers should be administered in advance to avoid the adrenergic crisis [82, 83]. MIBG therapy has been used in systemic treatment of select patients with metastatic pheochromocytoma [34].

Follow-up In adrenal incidentalomas (AIs) that are nonfunctioning or masses with size less than 4 cm, surveillance is advocated although no definite guidelines exist. The NIH 2002 state of science statement is accepted. It recommends

repeat imaging at 6 and 12 months following the initial identification of the mass [6, 43]. The role of imaging is in the assessment of radiologic status of the mass. Masses less than 1 cm and benign in appearance do not need any further follow-up. Similarly, the so-called benign masses like myelolipomas, hemorrhages, and cyst do not require any further evaluation. There is no evidence for repeat imaging for masses that do not increase in size. This is in view of the risk of developing malignancy due to radiation exposure. There is a very low risk of developing malignancy (0.1 %), subclinical hyperfunction (1.2 %), or overt disease (0.9 %) [40]. There is not much evidence for the rate of increase in size of mass predicting its malignant nature. But a 0.5–1.0-cm increase in size of the mass with suspicious features on imaging should be considered for surgical resection [5, 84]. Of the masses, 5–25 % will demonstrate an increase in size of greater than 1 cm and 2–8 % will become functioning with cortisol hypersecretion being the most common [85].

In AIs, functionality is assessed at yearly intervals for up to 4 years earlier if clinically indicated. Some studies recommend no further follow-up for lesions remaining stable on imaging or hormonal evaluation over a period of 4 years, while others suggest no follow-up if the mass remains stable over two imagings 6 months apart with no evidence of functionality [86].

In the case of ACC's post-resection, a diligent radiological follow-up to detect the high rate of locoregional and metastatic recurrence is required. Imaging of chest, abdomen, and pelvis is recommended at 3-month interval for the first 2 years. This interval is increased after 2 years but should be followed up at least for 5 years preferably more [85].

In conclusion, in view of the lack consensus on the follow-up protocols, clinicians should make clinical judgment keeping the recommendations and considering age and comorbidities of patient in mind.

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