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Clinical presentation of incidentally discovered adrenal tumors – our experience

Klinička prezentacija slučajno otkrivenih tumora nadbubrega – naša iskustva

Tamara Dragović*†, Valentina Mitrović-Jovanović‡, Saša Kiković*, Snežana Kuzmić-Janković*, Petar Ristić*†, Jelena Karajović*, Zorana Djuran*, Dejan M. Marinković*, Zoran Hajduković*†

Military Medical Academy, *Clinic for Endocrinology, Belgrade, Serbia; University of Defence, †Faculty of Medicine of the Military Medical Academy, Belgrade, Serbia; Military Hospital, ‡Department of Endocrinology, Niš Serbia

Abstract

Background/Aim. Incidentalomas of the adrenal gland are adrenal masses commonly discovered by chance on imaging not performed for suspected adrenal disease. The aim of this study was to analyze clinical, hormonal and histopathological characteristics of adrenal incidentalomas. **Methods.** This retrospective study included 85 patients (32 men and 53 women) examined for adrenal incidentalomas at the Clinic for Endocrinology, Military Medical Academy in Belgrade, from January 2013 to December 2017. The age of the patients, gender, size, and localization of adrenal tumors, functional activity, as well as the presence of comorbidities were analyzed. Adrenalectomy was performed in 35 patients due to its size and functional activity, and histological findings were analyzed. **Results.** The largest number (56.4%) of the adrenal tumors, was detected by ultrasound examination of the abdomen, 23 (27.2%) by abdominal computed tomography (CT) scan, 13 (15.2%) by chest CT scan and 1 (1.2%) by magnetic resonance (MR) imaging of the abdomen. The average tumor size was 3.8 ± 2.3 cm (range from 1 to 15 cm). Adrenal tumors were bilateral in 20 (23%) patients, in 39 (46%) patients, the tumors were localized in the right adrenal gland, and in 26 (31%) in the left gland. Subclinical hypercortisolism, defined as insufficient cortisol suppression during overnight dexamethasone test (1 mg), was observed in 34 (40%) patients, while the absence of cortisol suppression (autonomous cortisol secretion) was found in 4 (4.7%) patients. In the remaining 47 (55.3%) patients, complete overnight suppression of cortisol secretion was achieved. Thirty-five (41%) patients underwent adrenalectomy; among them, in 4 (11.4%) cases, adrenocortical carcinoma was found, 15 (42.9%) were adenomas, pheochromocytoma was found in 4 (11.4%) cases, nodular hyperplasia in 5 (14.3%) cases, distant metastasis in one (2.8%) case and the remaining were different benign masses. **Conclusion.** For patients with adrenal incidentalomas, two fundamental questions on determining the functionality of the tumor and/or the presence of malignancy need to be clarified. All patients with adrenal incidentaloma should undergo hormonal evaluation for autonomous or possible autonomous cortisol secretion, as well as for autonomous, adrenergic, and mineralocorticoid excess. In patients with autonomous adrenal secretion, surgery is indicated even if the typical clinical manifestation is absent.

Key words:
adrenal gland neoplasms; adrenal incidentaloma; diagnosis; surgical procedures, operative; histological techniques; ultrasonography.

Apstrakt

Uvod/Cilj. Incidentalomi nadbubrega su tumori nadbubrežne regije koji su slučajno otkriveni različitim radiološkim ispitivanjima, u toku dijagnostike oboljenja koja nisu povezana sa adrenalnom patologijom. Cilj rada je bio da se analiziraju kliničke, biohumoralne i histopatološke karakteristike adrenalnih incidentaloma. **Metode**. Retrospektivnom analizom bilo je obuhvaćeno 85 bolesnika (32 muškarca i 53 žena), koji su ispitivani na Klinici za endokrinologiju Vojnomedcinske akademije u Beogradu, u periodu od januara 2013. do decembra 2017. godine zbog incidentaloma nadbubrega. Ispitivani su životno doba bolesnika, veličina lokalizacija i funkcionalna aktivnost tumora, kao i postojanje komorbiditeta. Adrenalektomija je učinjena kod 35 bolesnika na osnovu tumorske veličine, hormonske aktivnosti i pridruženih bolesti. **Rezultati**. Najveći broj (56,4%) adrenalnih tumora otkriven je ultrazvučnim pregledom abdomena, kod 23 (27,2%) bolesnika putem kompjuterizovane tomo

Correspondence to: Dejan M. Marinković, Military Medical Academy, Clinic for Endocrinology, Crnotravska 17, 11 000 Belgrade, Serbia. E-mail: dejmarinkovic@gmail.com.

grafije (CT) abdomena, kod 13 (15,2%) bolesnika putem CT pregleda grudnog koša i kod 1 (1,2%) bolesnika pomoću magnetne rezonance abdomena. Prosečna veličina tumora iznosila je 3,8 ± 2,3 cm (raspon od 1 do 15 cm). Adrenalni tumori su bili bilateralni kod 23% bolesnika, kod 46% bolesnika su bili lokalizovani u desnom, a u 31% slučajeva u levom nadbubregu. Supklinički hiperkorticizam, definisan kao neadekvatna kortizolska supresija prekonoćnim deksametazonskim testom (1 mg) uočena je kod 34 (40%) bolesnika, dok je odsustvo kortizolske supresije (autonomna kortizolska sekrecija) pronađena kod 4 (4.7%) bolesnika. U preostalih 47 (55.3%) bolesnika ostvarena je kompletna prekonoćna supresija deksametazonom. Adrenelektomija je učinjena kod 35 (41%) bolesnika, među kojima je kod njih 4 (11,4%) dijagnostikovan adrenokortikalni karcinom, kod 15 (42,9%) adenomi, feohromocitom kod 4 (11,4%), nodularna hiperplazija kod 5 (14,3%), udaljena metastaza kod jednog (2,8%), dok se kod preostalih bolesnika radilo o različitim benignim masama. **Zaključak.** Kod bolesnika sa incidentalno uočenim tumorima nadbubrežne regije trebalo bi razjasniti dva osnovna pitanja: funkcionalni status tumora i/ili prisustvo malignoteta. Kod svih bolesnika bi trebalo sprovesti biohumoralno ispitivanje u smislu autonomne ili moguće autonomne kortizolske sekrecije, kao i ispitivanje autonomnog adrenergičnog i mineralokortikoidnog ekscesa. Kod svih bolesnika kod kojih postoji dokaz o autonomnoj sekreciji bilo kojeg hormona, neophodno je sprovesti radikalno lečenje, nezavisno od prisustva ili odsustva tipične kliničke manifestacije.

Ključne reči:
nadbubrežne žlezde, neoplazme; nadbubrežna žlezda, incidentalom; dijagnoza; hirurgija, operativne procedure; histološke tehnike; ultrasonografija.

Introduction

Adrenal incidentalomas are frequent endocrine disorders considered as the disease of modern technology, which lead to a marked increase of accidentally discovered tumors. By definition, these are asymptomatic adrenal masses detected on imaging not performed for suspected adrenal disease [1]. Adrenal incidentaloma is not a single clinical entity; this term includes a range of different pathological states common to being discovered by chance. Incidentalomas of the adrenal gland include a large number of histological diagnoses that originate from the adrenal medulla, cortex, or extra-adrenal tissues. According to the clinical features, these are most often nonfunctioning tumors, while a small number of patients exhibit a clinical presentation of enhanced secretion of one or more adrenal hormones. The initial diagnostic evaluation is aimed at revealing the functional status of the mass and the possibility of malignancy. For this reason, all patients with incidentally discovered adrenal masses must undergo a detailed clinical, biochemical and radiological assessment [2, 3].

The treatment of these patients depends on the tumor's functional activity, size, radiological characteristics and growth rate. The quality of life is another vital factor that influences the decision, but our knowledge about the impact of these tumors on quality of life is insufficient. According to the current guidelines, surgical treatment is recommended for adrenal masses larger than 4 cm in diameter, except in the case of clear benign lesions such as cysts or myelolipomas. Tumors smaller than 4 cm should be regularly laboratory and radiologically followed [1, 2].

The aim of this study was to analyze clinical and hormonal characteristics of adrenal masses, incidentally discovered and treated in our clinic during the five-year period, as well as the relationship with histopathological diagnosis in operated patients.

Methods

This retrospective study included 85 patients (32 men and 53 women), examined for incidentally discovered adrenal masses at the Clinic for Endocrinology, Military Medical Academy in Belgrade, from January 2013 to December 2017. The examination excluded patients with previously suspected adrenal functional adenomas or concurrent history of primary malignancies. We analyzed the age of the patients, gender, size and localization of adrenal tumors, previous examinations that led to the diagnosis of incidentaloma, functional activity, as well as the presence of concomitant arterial hypertension, diabetes mellitus, osteoporosis, dyslipidemia and obesity.

For assessing hormonal activity, we analyzed basal plasma adrenocorticotropic hormone and cortisol plasma values, overnight dexamethasone suppression test, serum dehydroepiandrosterone sulphate (DHEAS), serum testosterone and plasma concentrations of 17-beta estradiol, metanephrine and normetanephrine. Due to some technical incapacities, plasma aldosterone concentrations and plasma renin activity were performed only in patients with hypertension and accompanied hypokalemia, while daily urinary free cortisol and urinary 17-ketosteroids were not performed at all. The diagnosis of subclinical Cushing's syndrome (SCS) (silent Cushing's syndrome or possible autonomous cortisol secretion) was based on plasma cortisol levels after an overnight dexamethasone test (values between 50 nmol/L and 138 nmol/L). Patients with cortisol levels over 138 nmol/L after the overnight dexamethasone suppression were considered to have autonomous cortisol secretion. In patients with suspected mineralocorticoid excess, if the

aldosterone/renin ratio was greater than 20, autonomous aldosterone secretion was confirmed.

Adrenalectomy was performed in 35 patients due to tumor size (over 4 cm). Functional activities, comorbidities, and histological findings were analyzed.

Results

Eighty-five patients, 32 (37.5%) men and 53 (62.4%) women, were hospitalized for a five-year period for examining incidentally discovered adrenal masses. The average age of these patients was 59 ± 30 years (range from 28 to 79 years of age). Sixty-four (75%) patients were over 50 years old, with a peak in the seventh decade in 32 (38.5%) patients.

In 48 (56.4%) patients with adrenal incidentaloma, tumors were detected by an ultrasound examination of the abdomen, in 23 (27.2%) patients by abdominal computed tomography (CT) scan, in 13 (15.2%) patients by chest CT scan and in 1 (1.2%) patient by magnetic resonance (MR) imaging of the abdomen. The average tumor size was 3.8 ± 2.3 cm (range from 1 to 15 cm).

Adrenal tumors were bilateral in 20 (23%) patients, in 39 (46%) patients, adrenal tumors were localized in the right adrenal gland, and in 26 (31%) patients in the left gland.

The way of detecting adrenal tumors is shown in Table 1.

Table 1

Detection of adrenal incidentalomas

Indications for medical examination	Patients n (%)
Medical checkup (non-endocrine disorders)	21 (24.7)
Gastrointestinal symptoms	12 (14.1)
Pulmonary symptoms	12 (14.1)
Urinary symptoms	11 (12.9)
Stomach ache	13 (15.3)
Cardiovascular symptoms	7 (8.2)
Lumbar syndrome	5 (5.9)
Gynecology symptoms	2 (2.4)
Traumatic injury	2 (2.4)
Total	85 (100)

Subclinical hypercortisolism (SCS), defined as an insufficient cortisol suppression during the low dose overnight dexamethasone test (1 mg) (plasma cortisol between 50 and 138 nmol/L) was observed in 34 (40%) patients, while the absence of cortisol suppression (autonomous cortisol secretion) was found in 4 (4.7%) patients. In the remaining 47 (55.3%) patients, complete overnight suppression of cortisol secretion was achieved (plasma cortisol less than 50 nmol/L) (Table 2). In the group of patients with SCS, nearly 23 (74%) patients had accompanied arterial hypertension, 7 (20%) patients had type 2 diabetes, 5 (14.70%) had dyslipidemia, another 5 (14.7%) had osteoporosis and 20 (58.8%) were overweight or obese – body mass index > 25 kg/m^2. Normal values of basal plasma cortisol levels were found in 63 (53.6%) patients, while the values were elevated in the remaining 22 patients. Among them, 10 patients had SCS, 4 had autonomous cortisol secretion, and in 8 patients, complete suppression during the overnight dexamethasone test was found.

Table 2

Frequency of different types of adrenal incidentalomas (n = 85)

Type of adrenal incidentaloma	Patients n (%)
Nonfunctioning	41 (48.2)
Functioning	44 (51.8)
SCS	34 (40)
ACS	4 (4.7)
AAS	2 (2.4)
pheochromocytoma	4 (4.7)

SCS – subclinical Cushing´s syndrome;
ACS – autonomous cortisol secretion;
AAS – autonomous aldosterone secretion.

Cut-off values (more than 20) were reached in two patients, who underwent surgical adrenalectomy, and histopathologic examination confirmed adrenal cortical adenoma. After the surgical treatment, both patients remained normotensive and normokalemic.

Thirty-five (41%) patients underwent adrenalectomy; among them, adrenocortical carcinomas were found in 4 (11.4%) cases, 15 (42.9%) were adenomas, pheochromocytoma was found in 4 (11.4%) cases, nodular hyperplasia in 5 (14.3%) cases, distant metastasis (2.8%) in one case and the remaining were different benign masses (Figure 1). Of the 15 patients with adenomas, 2 had aldosteronoma, 7 had SCS, 3 had autonomous cortisol secretion and the rest had nonfunctioning adenomas.

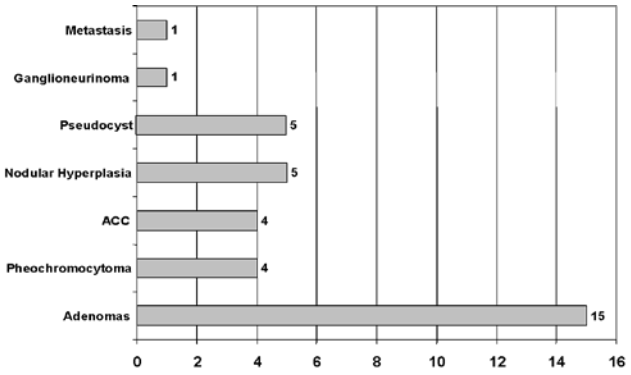

Fig 1. - Histological findings in operated patients.

ACC – adrenocortical carcinoma.

The surgical treatment was performed in 8 patients with SCS due to the tumor size (over 4 cm) and the presence of at least two comorbidities. In one operated patient, the histological analysis confirmed adrenocortical carcinoma; the rest were functional adenomas. Interestingly enough, 5

(75%) patients with SCS and mild arterial hypertension became normotensive after adrenalectomy, with no need for any further antihypertensive treatment.

Pheochromocytoma was found in 4 patients (1 male and 3 female) with an average age of 53 ± 13 years and average tumor size of 4.5 ± 3.1 cm (range from 1.8 to 6.1 cm). All of the patients had biochemical confirmation of autonomous adrenergic hypersecretion expressed by elevated plasma levels of metanephrine and normetanephrine. Hypertension was present in 75% of the patients. Adrenocortical carcinoma (ACC) was observed in 4 patients (2 male and 2 female), with an average age of 53 ± 9 years (range from 44–60 years of age) and an average tumor size of 7.9 ± 5.7 cm (range from 3.5 to 15 cm). Two patients had arterial hypertension, one was diabetic and one patient had autonomous cortisol secretion. Bilateral adrenal masses were found in 19 cases (22.3%). Of these patients, 10 had SCS, while the rest were nonfunctioning tumors. Among these, adrenalectomy of tumors over 4 cm in diameter was performed in 4 cases.

The results of histological analysis of patients operated on due to incidentally discovered adrenal tumors are shown in Figure 1.

Due to some technical inabilities, we performed measurement of aldosterone/plasma renin activity ratio in only three patients who had associated hypertension and hypokalemia. Cut-off values (more than 20) were reached in two patients who underwent surgical adrenalectomy and histopathologic examination confirmed adrenal cortical adenoma. After surgical treatment, both patients remained normotensive and normokalemic.

Discussion

The prevalence of randomly detected adrenal masses during the CT imaging is 3%–4%, with slightly greater incidence in women [4]. In autopsy studies, the frequency of these tumors varies depending on the patient's age and ranges from 1%–7.8% [5]. These tumors are rarely seen in people under 30 years of age (0.3%), with the highest incidence in people between 50 and 70 years of age. Adrenal incidentalomas are most often found in the right adrenal gland, 50%–60%, in the left adrenal gland, 30%–40%, and in 10%–15% of patients in both glands. The average size of these changes is 3–3.5 cm and ranges from 0.5 cm to 25 cm [4–7]. Similarly, in our investigated group 75.3% of the patients were over 50 years old, with a peak in the seventh decade in 38.5% of the patients. The average size of incidentaloma in our patient group was 3.8 cm ranging up to 15 cm in diameter and was most often localized in the right adrenal gland. A possible explanation for the higher incidence in older age is the more frequent use of radiological diagnostic imaging, as part of the evaluation of various diseases, or possible compensatory hyperplasia in response to local ischemia due to atherosclerotic changes in blood vessels [8].

Clinical evaluation of adrenal incidentaloma implies detailed history and physical examination in order to access clinical symptoms and signs of adrenal hormonal excess. Biohumoral investigation should focus on determining the existence of hypercortisolism, hyperaldosteronism, or autonomous sympathoadrenal hypersecretion. Radiological evaluation should be done to determine whether the incidentally revealed mass is benign or malignant. Most authors suggest that MR imaging has several advantages over the CT scan because of its lack of radiation exposure, iodine-based contrast media, and the superior tissue contrast resolution [5–8]. Yet, the current recommendations of the European Clinical Practice Guideline primarily suggest the use of non-contrast CT imaging in order to determine if the mass is homogenous [Hounsfield units (HU) ≤ 10] and lipid-rich and therefore benign[1]. Regardless of the way the incidentalomas were found, all patients in this series underwent adrenal non-contrast or contrast CT imaging.

According to clinical features, adrenal incidentalomas are most often nonfunctioning tumors, while in a small percentage of patients, the hypersecretion of one or more adrenal hormones is present. Interestingly, in this group of incidentalomas, there was a slightly higher frequency of functioning tumors (51.8%), while the patients with SCS were the most frequent. Literature data report a prevalence of 5%–24% for SCS in patients with adrenal incidentaloma [7–10]. This wide range could be partly explained by different diagnostic criteria for SCS. In our group of patients, the presence of SCS in 34 (47.3%) patients was observed, while the autonomous cortisol secretion was found in 4 (5.3%) cases. In the remaining 47 (47.4%) cases, complete overnight suppression of cortisol secretion was achieved. The risk of developing autonomous cortisol secretion without signs of overt Cushing's syndrome varies between 0%–11% of patients with adrenal incidentaloma [9, 10]. All four patients with autonomous cortisol secretion in this group had no convincing clinical signs of Cushing's syndrome.

Normal values of basal plasma cortisol levels were found in 63 (53.6%) patients, while the values were elevated in the remaining 22 patients. Among the patients with elevated cortisol levels at basal state, 12 patients had SCS, 4 had autonomous cortisol secretion, while in 4 patients, complete overnight suppressions were found. Normal values of basal cortisol levels do not exclude the presence of cortisol excess. In the group of patients with normal basal cortisol levels, SCS was observed in 10 cases, while the complete suppression of cortisol secretion was achieved in the remaining patients.

Patients with SCS should be considered individually. When deciding on further treatment, patients' age, general condition, presence of comorbidities and the degree of cortisol excess should be taken into account.

Adrenocortical carcinoma (ACC) is a rare malignancy with an incidence that ranges from 0.7–2 cases per million habitans/year, with the peak of occurrence between 40 and 50 years of age. In some series, malignancy was significantly associated with age, weight loss and increased tumor size [11]. Although steroid hormone excess is present in most ACC (40% to 60%), in 20% of cases, it is diagnosed incidentally [12]. Traditional imaging is able to correctly

diagnose an adrenal mass as ACC in most cases. The risk of ACC rises with age and tumor size. Index of suspicion increases for tumors over 4 cm in diameter (sensitivity 97%, specificity 52%) and over 6 cm (sensitivity 91%, specificity 80%). Most of the ACC are larger heterogeneous tumors due to the areas of necrosis, hemorrhage and calcification, usually with irregular margins [13]. Currently, a non-contrast CT scan is recommended as a mandatory imaging technique in suspicion of ACC. The threshold of ≤ 10 Hounsfield units (HU) for benign adrenal masses on non-contrast CT has been established by many studies. At the same time, the risk of malignancy in homogenous adrenal masses with 5 cm in diameter and non-contrast attenuation values of ≤ 10 HU is almost zero. When the basal density is more than 10 HU, contrast CT imaging should be performed; since the malignant adrenal lesions demonstrate a slower washout of contrast medium, an absolute washout of over 50% suggests a benign adrenal mass [13–15].

The benefit of MR imaging in the differential diagnosis of adrenal masses is less clear.

If the CT scan cannot perfectly differentiate the origin of adrenal masses, MR imaging could be useful in diagnosing ACC by the presence of isointense to hypointense signal on T1-weighted images; the hyperintense signal on T2-weighted images, and a heterogeneous signal drop on chemical shift [12].

According to the current guidelines, surgical treatment is recommended for adrenal masses larger than 4 cm in diameter, except in the case of clear benign lesions, such as cysts or myelolipomas. Tumors of less than 4 cm should be regularly laboratory and radiologically followed [1, 2].

In this series of adrenal incidentaloma, ACC was observed in 4 patients (2 male and 2 female), with the average age of 53 ± 9 years (range 44–60 years of age) and the average size of 7.9 ± 5.7 cm (range 3.5–15cm). Deciding upon the operative treatment was based on the tumor size in three patients (more than 4 cm) and on the typical radiological characteristics observed in contrast CT imaging in all four cases. Two patients with ACC were hypertensive, one was diabetic, and one patient had autonomous cortisol secretion.

The presence of pheochromocytoma should be excluded in all patients with adrenal incidentaloma, including those with normal blood pressure. About 30% of all pheochromocytoma are detected incidentally and their prevalence is increasing. Prevalence of pheochromocytoma in adrenal incidentalomas varies from 1% to 11%, according to different authors [4–7, 16]. In this study, there were 4 patients (11.4%) with pheochromocytoma with an average tumor size of 4.5 ± 3.1 cm (range 1.8–6.1 cm). Currently, there is a lack of consensus on the best initial diagnostic test for evaluating pheochromocytoma. Most authors recommend using plasma metanephrine as the initial diagnostic test due to its high diagnostic sensitivity. Plasma metanephrine levels 3 times higher than normal are highly diagnostic for pheochromocytoma (sensitivity 96%–100% and specificity 85%–89%) [16–18].

On contrast-enhanced CT imaging, pheochromocytoma may show homogenous or variable enhancement due to areas of cystic changes and hemorrhage. Contrast washout in pheochromocytoma may be variable and may overlap both benign or malignant lesions such as ACC, although a non-contrast CT of less than 10 HU is extremely rare in these tumors [19, 20]. Pheochromocytoma typically shows avid gadolinium enhancement in the MR imaging, but this could be variable depending on the presence of cystic or necrotic areas [21].

All our patients had biochemical confirmation of autonomous adrenergic hypersecretion expressed by elevated plasma levels of metanephrine and normetanephrine. All cases were confirmed by pathohistological examination. It is not unusual that incidentally discovered pheochromocytoma show no hypertension in clinical presentation [4, 16, 18]. The prevalence of normotensive pheochromocytoma in a series of adrenal incidentalomas ranges up to 50% [22, 23]. Deciding upon the surgical treatment was based on the radiographic characteristics of the tumor and the results of biochemical analysis, even though one patient had no hypertension.

The estimated prevalence of primary hyperaldosteronism in adrenal incidentaloma is less than 1%. In the examined group, there were two patients (2.4%) with autonomous mineralocorticoid excess. It is known that some of these patients can be normokalemic. Because of that, it is recommended that the screening for primary hyperaldosteronism be performed in all hypertensive patients with adrenal incidentalomas [1, 2, 24, 25].

Bilateral adrenal masses were found in 19 (22.3%) cases; of these, 10 patients had SCS, while the rest were nonfunctioning tumors. Unilateral adrenalectomy of larger tumors (over 4 cm in diameter) was performed in 4 cases. Since none of the SCS patients and bilateral adrenal masses had no clinical signs of overt Cushing´s syndrome, deciding upon the operative treatment was based on the tumor size and the presence of comorbidities. Among the operated masses, the histopathological analysis showed the presence of adenoma in all 4 patients.

In our study group, 35 patients underwent adrenalectomy. Surgical treatment was performed in all functioning tumors, those larger than 4 cm in diameter and those with suspicious radiological characteristics. In patients with SCS, surgical treatment was performed on large tumors, or if at least two comorbidities were present. Adrenalectomy was performed using laparoscopic surgery or open laparotomy. For adrenal masses that were suspected of malignancy, larger than 6 cm, and with signs of local invasion, open adrenalectomy was performed; for tumors without evidence of local invasion and less than 6 cm in diameter, laparoscopic surgery was performed. All patients with autonomous cortisol secretion and those with SCS received preoperative and postoperative glucocorticoid treatment for at least 6 months. Follow-up of operated patients is ongoing according to actual recommendations [1, 2, 26].

Conclusion

For patients with incidentally detected adrenal tumors, two questions on determining the tumor functionality and/or the presence of malignancy need to be clarified. The existence of typical clinical manifestation of hormonal excess is not

necessary for hormonal testing. All patients with adrenal incidentaloma should undergo hormonal evaluation for autonomous or possible autonomous cortisol secretion, as well as for autonomous, adrenergic, and mineralocorticoid excess. The radiologic evaluation most often refers to contrast medium washout on CT scan or tumor density on non-contrast CT imaging. Adrenal masses with suspicious radiologic characteristics, functional tumors, and those with more than 4 cm in diameter should undergo adrenalectomy. In patients suspected of having autonomous adrenal secretion, surgery is indicated even if the typical clinical manifestation is absent.

R E F E R E N C E S

1. *Fassnacht M, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A,* et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol 2016; 175(2): G1–G34.
2. *Zeiger MA, Thompson GB, Duh QY, Hamrahian AH, Angelos P, Elaraj D,* et al. American Association of Clinical Endocrinologists; American Association of Endocrine Surgeons. American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons Medical Guidelines for the Management of Adrenal Incidentalomas: executive summary of recommendations. Endocr Pract 2009; 15(5): 450–3.
3. *Barzon L, Sonino N, Fallo F, Palu G, Boscaro M.* Prevalence and natural history of adrenal incidentalomas. Eur J Endocrinol 2003; 149(4): 273–85.
4. *Zeiger MA, Siegelman SS, Hamrahian AH.* Medical and surgical evaluation and treatment of adrenal incidentalomas. J Clin Endocrinol Metab 2011; 96(7): 2004–15.
5. *Erdem H, Çetinkünar S, Kuyucu F, Erçil H, Görür M, Sözen S.* Surgical approach in adrenal incidentalomas: Report of thirteen cases and review of the literature. Ulus Cerrahi Derg 2015; 32(2): 103–6.
6. *Porcaro AB, Novella G, Ficarra V, Curti P, Antoniolli SZ, Suangwoua HS,* et al. Adrenal incidentalomas: surgical treatment in 28 patients and update of the literature. Int Urol Nephrol 2001; 32(3): 295–302.
7. *Luton JP, Martinez M, Coste J, Bertherat J.* Outcome in patients with adrenal incidentaloma selected for surgery: an analysis of 88 cases investigated in a single clinical center. Eur J Endocrinol 2000; 143(1): 111–7.
8. *Kim BY, Chun AR, Kim KJ, Jung CH, Kang SK, Mok JO,* et al. Clinical Characteristics and Metabolic Features of Patients with Adrenal Incidentalomas with or without Subclinical Cushing's Syndrome. Endocrinol Metab (Seoul) 2014; 29(4): 457–63.
9. *Terzolo M, Bovio S, Pia A, Osella G, Borretta G, Angeli A*, et al. Subclinical Cushing's syndrome. Arq Bras Endocrinol Metabol 2007; 51(8): 1272–9.
10. *Reincke M.* Subclinical Cushing's syndrome. Endocrinol Metab Clin North Am 2000; 29(1): 43–56.
11. *Lumachi F, Borsato S, Tregnaghi A, Marino F, Fassina A, Zucchetta P*, et al. High risk of malignancy in patients with incidentally discovered adrenal masses: accuracy of adrenal imaging and image guided fine-needle aspiration cytology. Tumori 2007; 93(3): 269–74.
12. *Libe R.* Adrenocortical carcinoma (ACC): diagnosis, prognosis and treatment. Front Cell Dev Biol 2015; 3: 45.
13. *Schteingart DE, Doherty GM, Gauger PG, Giordano TJ, Hammer GD, Korobkin M,* et al. Management of patients with adrenal cancer: recommendations of an international consensus conference. Endocr Relat Cancer 2005; 12(3): 667–80.
14. *Hussain S, Belldegrun A, Seltzer SE, Richie JP, Gittes RF, Abrams HL.* Differentiation of malignant from benign adrenal masses: predictive indices on computed tomography. AJR Am J Roentgenol 1985; 144(1): 61–5.
15. *van Erkel AR, van Gils AP, Lequin M, Kruitwagen C, Bloem JL, Falke TH.* CT and MR distinction of adenomas and nonadenomas of the adrenal gland. J Comput Assist Tomogr 1994; 18(3): 432–8.
16. *Leung K, Stamm M, Raja A, Low G.* Pheochromocytoma: the range of appearances on ultrasound, CT, MRI, and functional imaging. AJR Am J Roentgenol 2013; 200(2): 370–8.
17. *Chen H, Sippel RS, O'Dorisio MS, Vinik AI, Lloyd RV, Pacak K.* North American Neuroendocrine Tumor Society (NANETS). The North American Neuroendocrine Tumor Society consensus guideline for the diagnosis and management of neuroendocrine tumors: pheochromocytoma, paraganglioma, and medullary thyroid cancer. Pancreas 2010; 39(6): 775–83.
18. *Kopetschke R, Slisko M, Kilisli A, Tuschy U, Wallaschofski H, Fassnacht M,* et al. Frequent incidental discovery of phaeochromocytoma: data from a German cohort of 201 phaeochromocytoma. Eur J Endocrinol 2009; 161(2): 355–61.
19. *Hamrahian AH, Ioachimescu AG, Remer EM, Motta-Ramirez G, Bogabathina H, Levin HS,* et al. Clinical utility of noncontrast computed tomography attenuation value (hounsfield units) to differentiate adrenal adenomas/hyperplasias from nonadenomas: Cleveland Clinic experience. J Clin Endocrinol Metab 2005; 90(2): 871–7.
20. *Szolar DH, Kammerhuber F.* Quantitative CT evaluation of adrenal gland masses: a step forward in the differentiation between adenomas and nonadenomas? Radiology 1997; 202(2): 517–21.
21. *Lumachi F, Tregnaghi A, Zucchetta P, Cristina Marzola M, Cecchin D, Grassetto G,* et al. Sensitivity and positive predictive value of CT, MRI and 123I-MIBG scintigraphy in localizing pheochromocytomas: a prospective study. Nucl Med Commun 2006; 27(7): 583–7.
22. *Mansmann G, Lau J, Balk E, Rothberg M, Miyachi Y, Bornstein SR.* The clinically inapparent adrenal mass: update in diagnosis and management. Endocr Rev 2004; 25(2): 309–40.
23. *Grumbach MM, Biller BM, Braunstein GD, Campbell KK, Carney JA, Godley PA*, et al. Management of the clinically inapparent adrenal mass ("incidentaloma"). Ann Intern Med 2003; 138(5): 424–9.
24. *McAlister FA, Lewanczuk RZ.* Primary hyperaldosteronism and adrenal incidentaloma: an argument for physiologic testing before adrenalectomy. Can J Surg 1998; 41(4): 299–305.
25. *Fuller PJ.* Adrenal diagnostics: An endocrinologist's perspective focused on hyperaldosteronism. Clin Biochem Rev 2013; 34(3): 111–6.
26. *Lee JM, Kim MK, Ko SH, Koh JM, Kim BY, Kim SW*, et al. For the the Korean Endocrine Society, Committee for Clinical Practice Guidelines. Clinical Guidelines for the Management of Adrenal Incidentaloma. Endocrinol Metab (Seoul) 2017; 32(2): 200–18.

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