ACTA FACULTATIS
MEDICAE NAISSENSIS

UDC: 616.45-006-07
DOI: 10.5937/afmnai41-50244

Original article

Adrenal Incidentalomas: A Seven-Year Follow-Up Single-Center Experience

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SUMMARY

Introduction/Aim. Adrenal incidentalomas (AIs) are defined as tumours revealed during imaging procedures of abdomen or abdominal laparotomy, performed in patients without previous suspicion for adrenal disease. This study was conducted to evaluate morphological and functional features of AIs seven years after the initial diagnosis.

Patients and methods. Thirty-eight AI patients were monitored for seven years, with CT scans used for morphological follow-up. Hormonal activity assessments included basal cortisol levels, adrenocorticotropic hormone, overnight dexamethasone suppression test, plasma or urinary metanephrines, vanillymandelic acid, electrolytes, hematocrit, acid-base status, oral glucose tolerance test, and chromogranin A.

Results. Functional activity was confirmed in six patients, with mild autonomous cortisol secretion (MACS) detected in two patients. Nine patients underwent adrenalectomy. Histopathological examination revealed hormonal activity in six cases, adrenocortical carcinoma was found in one patient, while secondary deposits from bronchial carcinoma were detected in one patient. Among the remaining 29 patients observed for the first year, tumor size remained stable. After seven years, two patients experienced tumor enlargement ≥ 1 cm, along with the development of MACS on endocrine evaluation. Adrenalectomy was recommended for one patient due to tumor size exceeding 4 cm.

Conclusion. The initial adrenal incidentaloma (AI) evaluation must include comprehensive diagnostic procedures for surgical consideration. Subsequent follow-up should include CT imaging after 12 months to monitor the tumor growth. Although mild autonomous cortisol secretion does not tend to progress to overt Cushing's syndrome, it can develop in patients initially considered to have hormonally inactive tumor. Our findings suggest that even small adrenal masses (< 4 cm) can enlarge over seven years, potentially evolving into MACS. Therefore, regular long-term monitoring every 5 - 7 years is recommended.

Keywords: **adrenal incidentaloma, Cushing's syndrome, pheochromocytoma**

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INTRODUCTION

Adrenal incidentalomas (AIs) are defined as tumors revealed during imaging procedures of abdomen, performed in patients without previous suspicion for adrenal disease.

Due to technology advances and more frequent radiological imaging, the incidence of AI is remarkably increased (1). After the initial diagnosis is made, two crucial tasks are: 1. to evaluate if adrenal tumor is functional, and 2. to distinguish benign from malignant lesions. Although most AIs are benign, non-functional tumors (74% – 82.2%) abnormal hormonal secretion could be verified, reviling Cushing's' syndrome (CS 6% - 7%), pheochromocytoma (4.7% - 7.2%) or aldosteronomas (1.2% - 4.6%) (2 - 4). The frequency of malignant AIs is even lower, finding adrenocortical carcinoma (ACC) in 4.8% and metastatic lesions in 2.3% (2, 3, 5).

Many studies have been performed in order to establish the most precise and convenient diagnostic and therapeutic approach. While consensus for the initial assessments is made, there are still different suggestions and recommendations for long-term follow-up of the patients if the adrenal incidentaloma was not surgically removed.

AIM

This study was conducted to evaluate morphological and functional features of AIs after one and seven years of the initial diagnosis. The results could be helpful in preventing unnecessary, expensive diagnostic procedures, often performed too frequently.

PATIENTS AND METHODS

In a four-year period, 38 patients with adrenal incidentaloma (AI) were admitted at the Clinic of Endocrinology, Diabetes and Metabolic Disorders, Clinical Centre Niš. All the participants gave their informed consent and the study was approved by the Ethics Committee of the University Clinical Center Niš (Number 9391/1; 03. 04. 2022.). Adrenal tumor was revealed during abdominal CT/MRI performed without previous suspicion for adrenal disease. The following parameters were considered: patient age, gender, size and location of the tumor, as well as radiological characteristics of adrenal masses. In order to determine hormonal activity of incidentalomas, the following tests were done: basal cortisol values and day-night rhythm, adrenocorticotropic hormone (ACTH), 1 mg overnight dexamethasone suppression test (DST), vanillymandelic acid (VMA) in 24 h urine, electrolytes, haematocrit (HCT), acid-base status, oral glucose tolerance test (OGTT) and chromogranin A (CgA).

In patients with hypertension and unexplained hypokalaemia, aldosterone/renin ratio was measured in order to exclude primary aldosteronism. The patients highly suspicious of pheochromocytoma, underwent [131I]-meta-iodobenzylguanidine ([131I]-MIBG) scan, along with measurements of urinary or plasma metanephrines, parathyroid hormone (PTH) and calcitonin.

Indications for adrenalectomy were: diagnosed hormone excess, adrenal masses with radiological findings suspicious of malignancy and tumors ≥ 4 cm.

If AI was not surgically removed, the first control visualisation (CT/MRI) was performed after 12 months and the second one after seven years. Repeated hormonal work-up was conducted after one year and after seven years only if CT/MRI verified significant tumor enlargement or new clinical signs of endocrine activity appeared.

RESULTS

Patient's gender and age

Patients included 22 females (57.89%) and 16 males (42.1%). The youngest patient with diagnosed AI was 23 and the oldest was 78 years old. The highest incidence was in the sixth decade (39.47%, with similar percentage between genders, 21.05% females vs. 18.42% males) followed by the seventh decade (26.32%, with equal female-male percentage) and the fifth decade (21.05%, with higher percentage of females 18.42% vs. 2.63%). Both patients younger than 40 (5.26%) were females and three patients ol-

der than 70 years (7.89%) were males (Figure 1). Female patients were statistically significantly younger than males (50.86 ± 11.22 vs. 60.56 ± 8.47, $p < 0.01$). The majority of female patients were younger than 60, and most of the males were over 50 years old.

Tumor size and localization

Regarding the tumor localisation, 60.53% (23 patients) had tumor in the left adrenal gland, 31.56% (12 patients) in the right, and 7.89% (3 patients) had bilateral AI. The majority of analysed lesions were 1 cm to 4 cm in size (86.84%); only two patients (5.26%) had AI smaller than 1cm and three (7.89%) had visualised tumor mass larger than 4 cm (Figure 2).

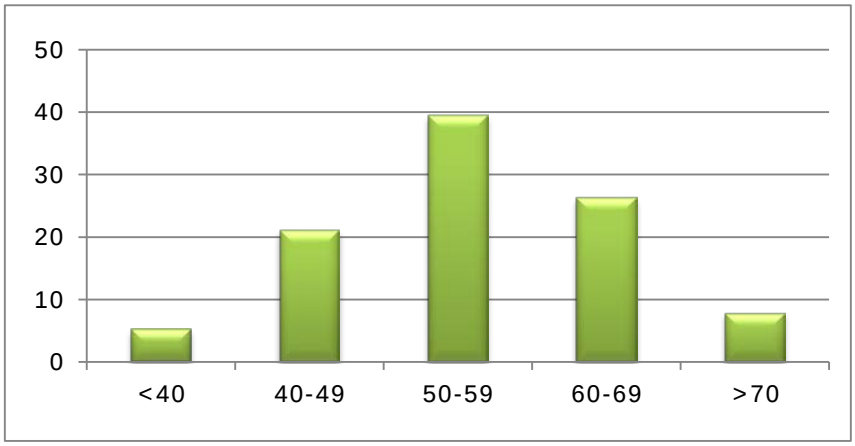

Figure 1. *Age distribution of patients with adrenal incidentalomas*

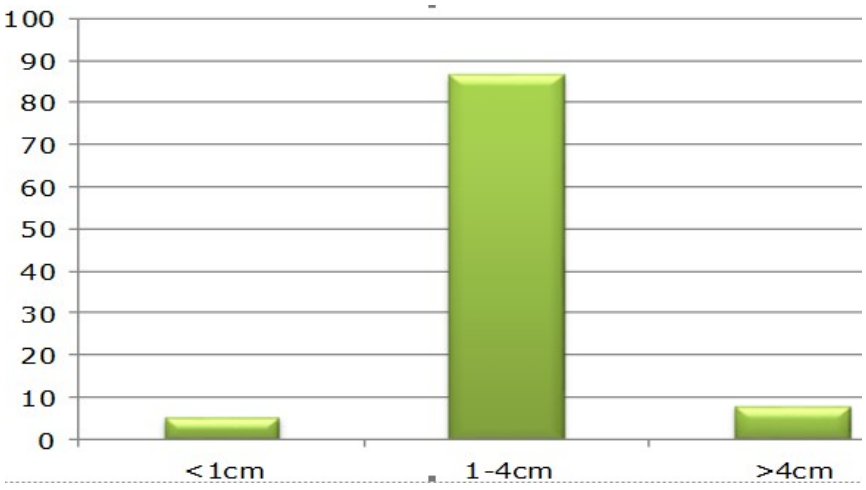

Figure 2. *The size of adrenal incidentaloma*

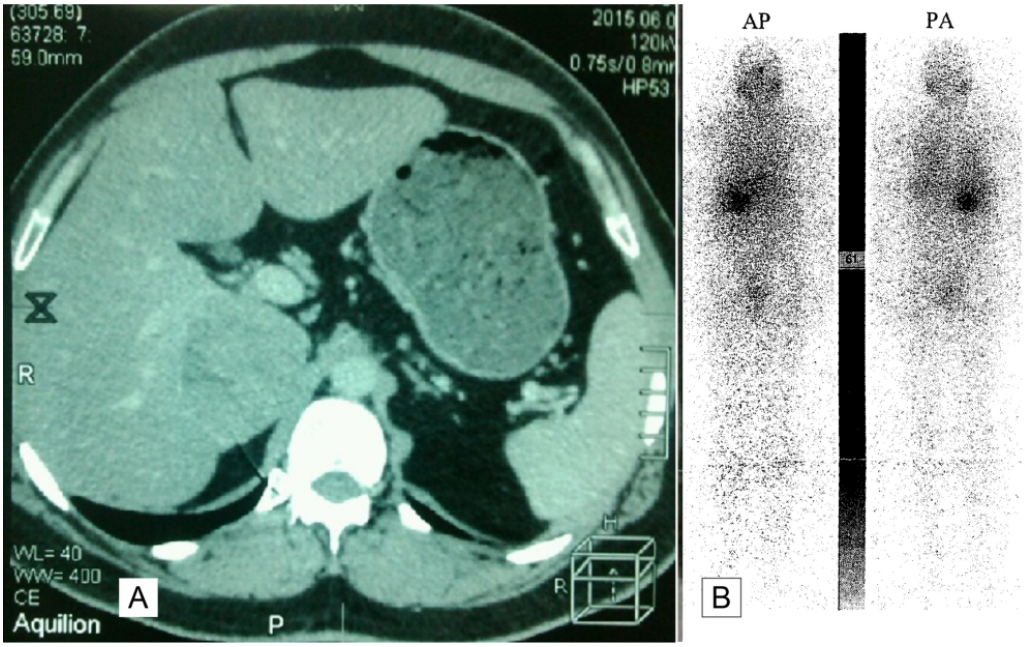

Figure 3. *Visualization diagnostic procedures: A. CT scan of the right adrenal tumor, transverse plane. B. [131I]-MIBG scan of the right adrenal pheochromocytoma*

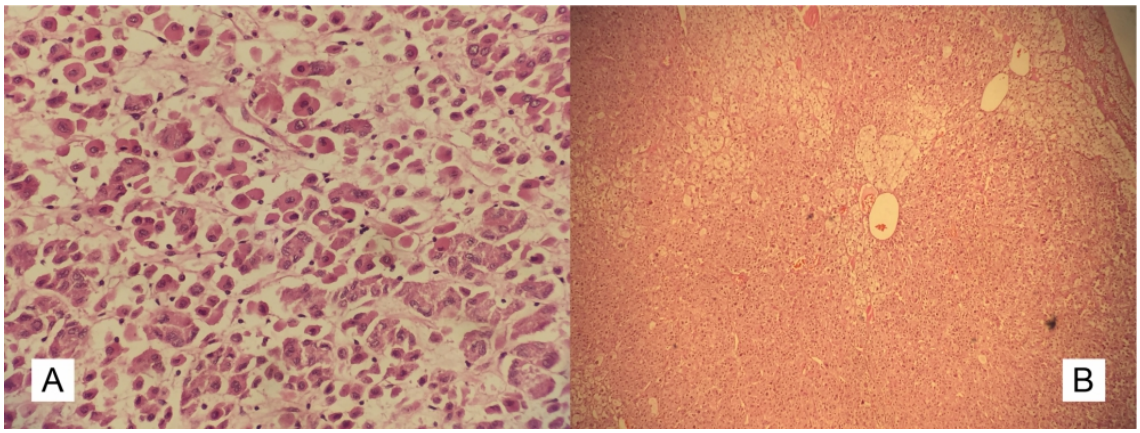

Figure 4. *Histopathological examination: A. Pheochromocytoma. B. Adrenocortical adenoma*

CT scan features

According to the CT features, only two patients (5.26%) had tumors highly suspicious of malignant AI, while the remaining 36 (94.74%) appeared like benign lesions. Among the patients with AI diagnosed as benign, 25 patients had CT characteristics of adenoma, six patients had lipoma and five patients had cystic/pseudocystic lesions. Based on radiological features which were indicative for pheochromocytoma, [131I]-MIBG scan was performed in five patients, confirming pheochromocytoma in three patients (Figure 3).

Hormonal evaluation

The majority of the patients (84.21%) had non-functional adrenal tumors. Among six patients (15.79%) with verified AI functional activity, three had pheochromocytomas, two were diagnosed as Cushing's syndrome and one patient had aldosterone-producing adenoma.

Only one patient with pheochromocytoma had discrete elevated VMA level, two had increased CgA and one had increased urinary metanephrines.

Both patients with Cushing's syndrome were first diagnosed as pre-eclampsia. The pregnancies

were terminated with an emergency caesarean section in the 28th/30th gestation week due to severe and uncontrolled hypertension. Few months after delivery, thorough diagnostic procedures were conducted. High cortisol levels, no suppression after 1 mg dexamethasone test and decreased ACTH, along with CT confirming adrenal tumors were diagnostic for the Cushing's syndrome.

Only one patient needed further hormonal investigation due to hypokalaemia, where increased aldosterone/renin ratio verified the Conn's syndrome.

Besides six patients with diagnosed hormonal activity of AI, two patients (5.26%) had mild autonomous cortisol secretion (MACS) previously called "subclinical Cushing's syndrome" and/or "autonomous cortisol secretion". Diagnostic criteria were: 1. biochemical evidence of cortisol excess (without ACTH suppression); 2. lack of specific clinical signs of Cushing's syndrome, and 3. post-dexamethasone serum cortisol levels > 5.0 μg/dL (> 50 nmol/L).

Adrenalectomy was performed in nine patients. Indications for surgical removal among our patients were: 1. functional activity, verified in six patients; 2. tumor highly suspicious on carcinoma (two patients), and 3. tumor size larger than 4 cm (one patient).

Histopathological examination confirmed suspected hormonal activity in six patients, adrenocortical carcinoma in one patient and secondary deposits due to bronchial carcinoma in one patient. Pheochromocytoma was composed of large cells, pink to mauve, arranged in cords or nests with capillaries in between (HE x 200) (Figure 4A) and adrenocortical adenoma had large cells with distinct cell borders arranged in clusters and abundant foamy cytoplasm (HE x 40) (Figure 4B).

First year follow-up

The first follow-up for the remaining 29 patients was after 12 months. None of the patients had enlargement of the tumor. Hormonal examination revealed no changes in the functional activity. Even two patients with MACS did not have any clinical or laboratory changes, which could indicate progression to the Cushing's syndrome.

Seven-year follow-up

After seven years, two patients had tumor enlargement and both of them developed MACS.

Patient 1. The functional assessment revealed mild autonomous cortisol secretion (MACS), as the 1 mg overnight dexamethasone suppression test (DST) failed to suppress cortisol below 50 nmol/L. ACTH dependence was ruled out. Comorbidities were investigated, revealing impaired glucose tolerance (IGT), normal electrolyte levels, and normotension with existing cardiac therapy. MRI abdomen during hospitalization showed enlargement of the previously described left adrenal gland lesion, now exceeding 4 cm with over 20% enlargement in the anteroposterior (AP) projection, surpassing 5 mm. Based on these findings, surgical intervention was deemed necessary due to significant tumor progression (Table 1.)

Patient 2. The functional examination revealed mild autonomous cortisol secretion (MACS) as the 1 mg overnight dexamethasone suppression test (DST) failed to suppress cortisol below 50 nmol/L, ruling out ACTH dependence. Comorbidities were investigated, showing no diabetes or glucose tolerance disorder, normal electrolyte levels, and normotension with the existing cardiac therapy. During hospitalization, MRI of the abdomen detected discreet enlargement of the previously described changes in the left adrenal gland, with no enlargement exceeding 4 cm, less than 20% enlargement in the largest diameter, and none exceeding 5 mm. Based on the examination, operative treatment is currently unnecessary, with only monitoring of adrenal gland tumor changes recommended. Schedule an MRI of the abdomen (adrenal glands) in one year (Table 1.)

Table 1. *Patients with tumor enlargement after a seven-year follow-up*

	Initial results		First year follow-up		Seven year follow-up	
	tumor size	hyperfunction	tumor size	hyperfunction	tumor size	hyperfunction
Patient 1	36x33 mm	not present	36x34 mm	not present	47x48 mm	MACS (cortisol 68.3 nmol/L after 1 mg DST)
Patient 2	22x23 mm	not present	28x22 mm	not present	32x31 mm	MACS (cortisol 62.1 nmol/L after 1 mg DST)

MACS-mild autonomous cortisol secretion

DISCUSSION

In the present study, slightly higher percent of patients with AI were females (57.89%) than males (42.1%). Studies based on autopsy reported similar incidences of adrenal tumors with no difference between genders (6, 7). However, this discrepancy in clinical settings probably reflects the fact that imaging procedures are more often performed in the female population. More frequent radiological examinations during the generative period of women, such as pregnancy, and during premenopause and menopause, can explain this study result of significantly younger female patients with AI compared to males.

Our study results showed that the tumor masses were more frequently detected in the left adrenal gland (60.53%) compared to the right (31.56%) and occurred bilaterally in 7.89% of cases. Kim at al. in their study on 348 patients with AI reported similar results regarding the higher incidence of the left side AI (3). Rashed at al. showed that adrenal gland tumors as second primary tumors were more frequently localized in the left adrenal gland (51.3%), followed by the right side (39.3%) (8). Although the adrenal glands are symmetrical, the left one is in a more caudal position. Their rich vascularization could be the reason for predilection of cancer metastases to the adrenal gland. Venous drainage differs between the left and right adrenal gland: the left suprarenal vein drains into the left renal vein, while the right suprarenal vein drains directly into the inferior vena cava. The various reported variations in venous drainage outlined in the literature hold significance not only for the surgical approach to adrenal tumors but also for diagnostic vein sampling (9). It remains within the realm of hypothesis whether these anatomical disparities could be the underlying cause for the higher incidence of left-sided adrenal tumours. More rational explanation for such results could be found in many radiological studies, which also observed higher prevalence of left-sided adrenal tumors, with an explanation that left adrenal gland and the left-sided adrenal tumors are more accessible and visible to the radiologist (10). A large cross-sectional study of abdominal CT and MRI imaging in 1,376 patients detected a higher incidence of the left-sided AI but only when the tumor size was smaller than 30 mm. The authors concluded that this detection bias may result in under-recognition of small (< 30 mm) right-sided lesions and bilateral disease (11).

Adrenal tumor size and homogeneity are considered to be most crucial data provided by non-contrast CT used to determine benign AI. Numerous clinical and imaging studies reported direct positive correlation between tumor size and malignancy (1, 3, 10). Analysing all available data from the literature, the European Society of Endocrinology (ESE) in the Clinical Practice Guideline recommended the tumor size cut-off < 4 cm, indicating that larger masses were less likely to be benign (12, 13). In this study, only three patients (7.89%) had adrenal tumor larger than 4 cm. All three underwent adrenalectomy. Surgical pathology findings were: adrenocortical carcinoma, pheo-chromocytoma and benign adenoma. The highest frequency of our patients had tumor mass with the size between 1 cm and 4 cm (86.84%). Six of them underwent surgery with the following histopathological outcomes: secondary deposits due to bronchial carcinoma in one patient, pheochromocytoma in two and adrenocortical adenoma in three patients (one with aldosterone-producing adenoma and two with glucocorticoid-producing adenoma).

Beside tumor size, non-contrast CT provides measurement of Hounsfield units (HU). The density of the lesion or mass found on the CT scan is com-

pared against the density of water, which is assigned the value of 0 HU. When the HU measurements are ≤ 10, tumors are considered to be homogeneous, lipid rich and very likely benign (12). HU values greater than 20 are highly suspicious of malignancy (13, 14). The majority of the patients in this study had HU measurements less than 10 units (33 patients; 86.84%). Among them, only one had tumor larger than 4 cm, which was an indication for adrenalectomy. Final histological finding was consistent with benign lesion. Even though three patients had detected adrenal tumor smaller than 4 cm with HU less than 10 units, which is strongly consistent with benign lesions, adrenalectomy was performed due to diagnosed functional activity (two patients had diagnosed Cushing's syndrome and one had Conn's syndrome). These findings are consistent with previously reported data that cortical adenomas are usually presented as benign lesions. One of the weaknesses of this diagnostic tool is that CT scans cannot determine if an adrenal mass is hyperfunctional or not (15). Another differential diagnostic dilemma, based on CT scans findings, arose in two patients with tumor size larger than 4 cm and HU greater than 20 units. Both lesions had similar CT description: inhomogeneous masses with heterogeneous cystic and necrotic areas. After administration of intravenous contrast, both had similar pattern of inhomogeneous contrast captivity, one lesion had irregular and the other well defined margins. As Kim et al. in their study pointed out, the tumor mass larger than 4 cm with HU higher than 20 units strongly suggests the diagnosis of malignant disease or pheochromocytoma (3). Even though patients with such CT scans findings are always indicated for surgery, it is crucial to determine a precise diagnosis before surgery because of the strict preoperative medication which is absolutely necessary for pheochromocytoma. Actual ESE guidelines for the management of adrenal incidentalomas recommend excluding pheochromocytoma by measurement of plasma-free metanephrines or urinary fractionated metanephrines (12, 13). In the situation where plasma-free metanephrines and urinary fractionated metanephrines were normal, which was the case in our two patients, we found it very helpful to conduct [131I]-meta-iodobenzylguanidine ([131I]-MIBG) scan, which revealed large area of increased uptake above the right kidney indicating giant right adrenal pheochromocytoma in one patient. There were four patients in total who underwent [131I]-MIBG scan. In the category of lesions smaller than 4 cm, with HU higher than 10, this slightly forgotten and neglected procedure was also very useful in pheochromocytoma diagnosis; metanephrines remained in the reference range.

Based on the functionality of adrenal lesions, it was observed that majority of the patients (84.21%) had non-functional adrenal tumors, while 15.79% had functionally active AI. Among six patients with verified AI functional activity, three had pheochromocytoma (7.89%), two were diagnosed as Cushing's syndrome (5.26%) and one patient had aldosterone-producing adenoma (2.63%).

In our study results, pheochromocytomas were the most frequently observed functional AIs, similar to previously published data, which reported between 7.2% and approximately 8% pheochromocytoma in their series (3, 16). Beside urinary metanephrines, which was elevated only in one patient with pheochromocytoma, we measured VMA in 24 h urine (also increased in one patient) and CgA (which was above normal referent range in two patients). In all three patients, as it was mentioned earlier, we conducted [131I]-meta-iodobenzylguanidine scan and found it very useful in preoperative diagnosis.

Both patients with Cushing's syndrome were pregnant and the first was diagnosed as preeclampsia. The pregnancies were terminated with an emergency caesarean section in the 28th/30th gestation week due to severe and uncontrolled hypertension. Few months after delivery, thorough diagnostic procedures were conducted. High cortisol levels, no suppression after 1 mg dexamethasone test and decreased ACTH, along with CT confirming adrenal tumors, were diagnostic of Cushing's syndrome. Besides six patients with diagnosed hormonally active AI, two patients (5.26%) had mild autonomous cortisol secretion (MACS) previously called "autonomous cortisol secretion" or "subclinical Cushing's syndrome". Both of them had no clinical signs of Cushing's syndrome, with high cortisol and normal ACTH, while post-dexamethasone serum cortisol levels were higher than 50 nmol/L.

Only one patient (2.63%) needed further hormonal investigation due to hypokalaemia, where increased aldosterone/renin ratio verified Conn's syndrome. Among functional AIs, aldosteronomas are usually tumors with the smallest incidence in the range from 1.2% - 4.6% in different series of patients, which is consistent with our study results (2, 3, 16). Possible explanation is that most aldosteronomas are

sized 1cm to 2 cm and therefore, usually determined clinically, due to arterial hypertension (often refractory to the therapy) and severe hypokalaemia, and then are located by CT (2, 3, 16, 17).

The first follow-up for the remaining 29 patients who did not undergo adrenalectomy was conducted after 12 months. None of the patients had enlargement of the tumor. Hormonal examination revealed no changes in the functional activity. Two patients with autonomous cortisol secretion did not have any clinical or laboratory changes, which could indicate progression to the Cushing's syndrome.

After seven years, patients with MACS did not have any worsening of arterial hypertension, onset of diabetes mellitus or marked changes in the lipid status. However, we noticed a slight increase of BMI in both of them (from 25 kg/m^2 and 29 kg/m^2 up to 28 kg/m^2 and 31 kg/m^2, respectively). The current ESE recommendation for AI follow-up is that no further imaging follow-up is required for adrenal mass < 4 cm with clear benign features (12, 13). Since the quality of evidence behind this recommendation is classified as very low, we performed follow-up CT scans after seven years and verified tumor in two patients. Control endocrine evaluation revealed mild autonomous cortisol secretion (MACS) in both patients. The current recommendations are against the hormonal work-up in patients with normal hormonal findings at initial evaluation unless new clinical signs of endocrine activity appear (13). Despite well-controlled hypertension and normal electrolyte levels, both patients with significant tumor enlargement showed mild autonomous cortisol secretion (MACS), with only one exhibiting impaired glucose tolerance (IGT) on OGTT.

CONCLUSION

Due to technological advances, the frequency of adrenal incidentalomas is constantly increasing. The majority of AIs is non-functional. First AI evaluation has to include thorough diagnostic procedures in order to triage patients for surgical treatment. If adrenalectomy is not indicated, further follow-up should contain CT visualisation after 12 months to exclude significant tumor growth. While patients with mild autonomous cortisol secretion (MACS) have no tendency in progression to overt Cushing's syndrome, it is important to note that MACS can also develop in patients initially deemed hormonally normal. Our findings indicate that even initially small adrenal masses (< 4 cm) with benign features can enlarge over a seven-year follow-up, potentially evolving into MACS. Hence, it is advisable to conduct regular long-term monitoring every 5 - 7 years.

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Article info
Received: April 4, 2024
Revised: April 19, 2024
Accepted: April 19, 2024
Online first: May 22, 2024

Sedmogodišnje praćenje bolesnika sa adrenalnim incidentalomom: iskustvo jednog centra

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SAŽETAK

Uvod/Cilj. Adrenalni incidentalomi (AI) definišu se kao tumori koji su radiološkim procedurama ili abdominalnom laparotomijom otkriveni kod bolesnika kod kojih prethodno nije postojala sumnja na bolest nadbubrežnih žlezda. Studija je sprovedena sa ciljem da se procene morfološke i funkcionalne karakteristike AI sedam godina nakon inicijalne dijagnoze.
Bolesnici i metode. Trideset osam bolesnika sa AI bilo je praćeno u periodu od sedam godina. Za morfološko praćenje koristila se kompjuterizovana tomografija (engl. *computerized tomography* – CT). Za procenu hormonske aktivnosti korišćene su sledeće analize: bazalni nivo kortizola, adrenokortikotropni hormon, prekonoćni (1 mg) deksametazonski supresioni test, metanefrin u plazmi ili urinu, vanilmandelična kiselina, elektroliti, hematokrit, acido-bazni status, oralni test tolerancije na glukozu i hromogranin A.
Rezultati. Funkcionalna aktivnost tumora otkrivena je kod šest bolesnika, dok je kod njih dvoje potvrđeno postojanje umerene autonomne sekrecije kortizola (engl. *mild autonomous cortisol secretion* – MACS). Adrenalektomija je urađena kod devet bolesnika. Histopatološko ispitivanje pokazalo je hormonsku aktivnost tumora kod šest bolesnika, adrenokortikalni karcinom kod jednog bolesnika, kao i sekundarne depozite bronhijalnog karcinoma kod jednog bolesnika. Kod preostalih 29 bolesnika kontrolnim ispitivanjem posle godinu dana utvrđeno je da veličina tumora nije promenjena. Nakon sedam godina, kod dva bolesnika tumorsko uvećanje bilo je ≥ 1 cm, a endokrinološkim ispitivanjem verifikovan je MACS. Adrenalektomija je indikovana kod jednog bolesnika budući da je veličina tumora bila veća od 4 cm.
Zaključak. Inicijalna evaluacija AI podrazumeva opsežne dijagnostičke procedure koje se sprovode sa ciljem da se utvrdi da li je potrebno hirurško lečenje ili nije. Ukoliko nije, prva CT kontrola radi se nakon 12 meseci kako bi se pratio eventualni rast tumora. Mada MACS ne pokazuje tendenciju progresije u Kušingov (Cushing) sindrom, može se razviti i kod bolesnika koji su na inicijalnom ispitivanju imali hormonski neaktivan tumor. Rezultati našeg ispitivanja pokazuju da čak i mali adrenalni tumori (< 4 cm) u periodu od sedam godina mogu značajno porasti i razviti umerenu autonomnu sekreciju kortizola. Stoga, dugoročno praćenje ovih bolesnika u intervalima od pet do sedam godina nesumnjivo je potrebno.

Ključne reči: **adrenalni incidentalomi, Kušingov sindrom, feohromocitom**