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Brankica KRSTEVSKA[1], Zivko POPOV[2]

DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH ADRENAL INCIDENTALOMAS: OUR EXPERIENCE

Abstract

Introduction: Adrenal incidentalomas (AIs) are adrenal masses which are incidentally discovered with imaging technology. They are non-functional and functional, benign, and malignant lesions.

Aim: We present a 5-year study of diagnostic and follow up of adrenal incidentalomas with special emphasis on their hormonal activity and differentiation from benign to malignant masses.

Material and methods: A group of 26 patients with AIs were investigated at the Internal Medical Centre "Srce". In all patients, clinical examination, CT, and hormonal tests were performed.

Results: Of the 26 patients (10 male and 16 female), aged between 25 and 80, the median tumour size was 33 mm, unilateral AIs in 96.1%, located on the right side in 52%, 96% were benign masses, of which 81% were non-functional adrenal masses. Non-functional asymptomatic autonomous cortisol secretion tumours were 22.2%, 7.7% were pheochromocytoma, 3.8% was Cushing's syndrome, adrenocortical carcinoma in 3.8%, and Schwannoma in 3.8%. Statistically significant positive correlation was found between HTA and secreting adrenal tumours ($r=0.426$, $p<0.05$), and between the post- suppressive level of cortisol and the size of adrenal tumour ($r= 0.560$, $p<0.05$). Age, symptoms and DMT2 have statistically significant impact on the prediction of

[1] Internal Medicine Centre "Srce", Skopje; Medical Faculty, University "SS Cyrill and Methodius", Skopje, North Macedonia

[2] Macedonian Academy of Science and Arts, Skopje; Medical Faculty, University "SS Cyrill and Methodius", Skopje, North Macedonia

tumour masses larger then 4 cm ($p<0.05$). 53.8% of patients underwent surgery and the others are followed.

In this small study of 26 cases with AIs, 11.5% were benign hyper-secreting tumours, and only one patient (3.8%) had a malignant tumour. Appearance of symptoms, age, or tumour masses larger than 4 cm are more likely to be secreting or malignant tumours.

Keywords: adrenal incidentalomas, pheochromocytoma, "autonomous cortisol secretion", tumour size.

Introduction

Adrenal incidentalomas (AIs) are adrenal masses, generally 1 cm or more in diameter, discovered incidentally with radiological examination, performed for other medical indication than adrenal diseases [1]. With modern radiological imaging techniques such as abdominal ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI), this entity appears more frequently in clinical practice and causes more clinical dilemmas [2]. The prevalence of AIs on autopsy series was reported to be about 8%, and 4% on the radiological series with a tendency to increase in the future [3, 4]. The prevalence rises with ageing. AI affects about 0.2% of patients between 20 and 30 years of age, while it affects 7% of patients over 70 years of age. This entity is a more common disease between the ages of 50 and 70 years mainly in patients with diabetes mellitus type 2 (DMT2), hypertension (HTA), and obesity. In an ageing society, this problem will become a more frequent risk in diagnosis and management.

AIs are benign or malignant and non-functional or functional tumours. The differential diagnosis includes a non-functioning adrenal adenoma, functional tumours (Cushing's syndrome, pheochromocytoma, primary aldosteronoma), primary adrenocortical carcinomas, metastases, and other adrenal masses (myelolipoma, cyst, Schwannoma, ganglioneuroma) [5]. They should be managed based on the functional status and the potential for malignancy. Primary adrenocortical carcinomas are rare, but metastases from extra adrenal carcinomas (lung, breast, colon, melanoma, lymphoma) are more common. Some of these lesions may be identified easily, but it is

difficult to distinguish adenoma from carcinoma. In the past two decades, the growing literature of data has allowed for recommendations of diagnosis and for decisions to be developed, such as how to treat AIs, based on clinical, hormonal and radiographic testing [1, 7]. The tumour size and radiological appearances are two key predictors for malignant AIs. Adrenal masses ≥ 4 cm or radiologically suspicious AIs are recommended for removal with total adrenalectomy. Functional tumours (Cushing's syndrome, pheochromocytoma, primary aldosteronoma) need urgent therapy. Non-functional adrenal incidentalomas may be asymptomatic hypersecreting adenoma known as autonomous cortisol secretion (subclinical Cushing's syndrome) with a high risk for morbidity and for surgery [7, 8]. Small and non-functional ones predominate in AIs and they should be followed-up.

Material and methods

In this retrospective study, conducted from September 2015 to September 2020, at the Internal Medicine Centre "Srce", Skopje, 26 patients were admitted with adrenal masses incidentally discovered via radiological imaging techniques. Evaluation of all patients with adrenal incidentaloma includes clinical, hormonal, and radiological testing.

Careful history was taken and physical examinations were performed which looked for the symptoms and signs of adrenal hormonal excess (Cushing's syndrome, pheochromocytoma, aldosteronism) and malignant disease in patients with AI.

Demographic characteristics of the patients were: age, sex, diameter and side of the lesion, endocrine function, BMI, type 2 diabetes mellitus, hypertension, histological findings from surgical adrenalectomy, or follow- up.

The following hormonal tests were performed: measurement of basal cortisol and basal adrenocorticotropic hormone (ACTH), in a fasting state at 8:00 AM. Out of 26 patients, 18 with AIs underwent a 1- mg dexamethasone suppressive test. The criteria for cortisol over secretion [1, 5] were: post-dexamethasone serum cortisol level at <50 nmol/l is considered “normal”; post-dexamethasone serum cortisol level between 51 to 138 nmol/l indicates “possible autonomous cortisol secretion” and a level of cortisol above 138

nmol/l suggests “autonomous cortisol secretion”. The basal level of ACTH < 10 pg/ml confirms an “autonomous cortisol secretion”.

A urine collection after 24 hours for metanephrine and vanillyl-mandelic acid (VMA) was used for the evaluation of adrenal medulla.

CT, as the radiological method, was used primarily in detecting adrenal lesions and in distinguishing benign from malignant lesions.

Laparoscopic adrenalectomy was indicated in adrenal lesions > 4 cm with radiological characteristics consistent to malignancy, functional tumours and autonomous cortisol secretion.

The study was done according to the Helsinki Declaration.

Statistical Analysis.

Data are presented as average, median and percentages. The results were analysed with SPSS, version 21. Pearson correlation tests and the general linear model were used. The level of significance was set to $p<0.05$.

Results

Our study included 26 patients (16 female and 10 male), at a mean age of 54.5 ± 15.7 (range, 25-80) years (Table 1). Six patients were younger than 40, and 20 were older than 40 years. The number of patients with adrenal masses according to age was: 2 patients between 20 and 29 years; 4 patients between 30 and 39 years; 5 patients between 40 and 49; 4 patients between 50 and 59; and 11 patients were >60 years or older (Figure 1).

Table 1.

Demographic, clinical, hormonal, and radiological characteristics of patients with adrenal incidentalomas

No of patients	26
mean age (years)	54.5±15.7
female/male	16/10 (1.6)
Tumor size (median, mm)	33
Unilateral	25/26 (96.1%)
right	13/25 (52%)

left	12/25 (48%)
Bilateral	1/26 (3.8%)
cortisol (nmol/l)	449.8±155.5
1mg-DST (without suppression, cortisol>138nmol/l)	4/18 (22,2%)
1mg-DST (suppression between 50−138nmol/l)	5/18 (27.7%)
1mg-DST (suppression <50nmol/l)	9/18 (50%)
ACTH (pg/ml)	23.3±16.3
VMA (median, umol/dU)	31
metanephric (median, umol/dU)	2.15
BMI (kg/m2)	26.59±3,89
BMI>25kg.m2	15/26 (57%)
DMT2	6/26 (23.06%)
HTA	12/26 (46.1%)
with symptoms	20/26 (76.9%)
operat.	14/26 (53.8%)
Tu secreting Cushing	1/26 (3.8%)
Pheochromocytoma	2/26 (7.7%)
malignant (adenocarcinoma)	1/26 (3.8%)
incident of death during 5 years	2/26 (7.7%)

Presented results are averages ±SD and percentages. Abbreviations: 1mg-DST = 1mg dexamethasone suppressive test; ACTH=adrenocorticotropic hormone VMA=Vanillylmandelic acid BMI=body mass index; DMT2=diabetes mellitud type 2; HTA= arterial hypertension.

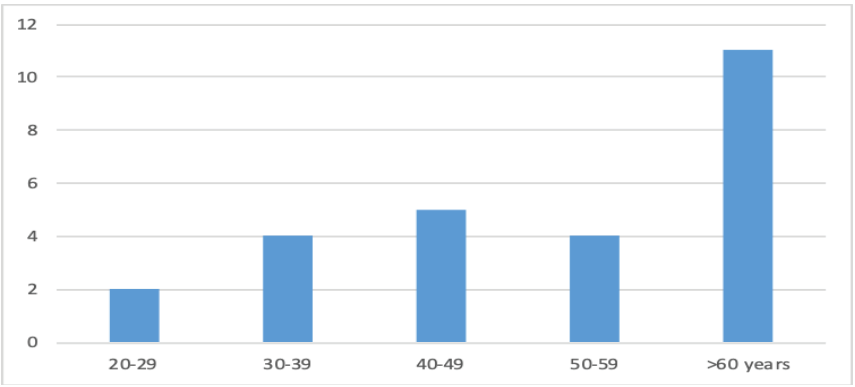

Figure 1 – Number of patients with adrenal masses according to age

Most of the patients had unilateral adrenal incidentaloma (96.1%) and only one patient (3.8%) had bilateral adrenal incidentalomas. Thirteen patients (52%) had adrenal incidentalomas located on the right side, 11 (42.2%) on the left side, and 1 had (3.8%) bilateral incidentalomas. The median size of the tumour was 33 mm (range 1-12cm). Fourteen patients had adrenal masses smaller than 40 mm, and twelve larger than 40 mm (Figure 2).

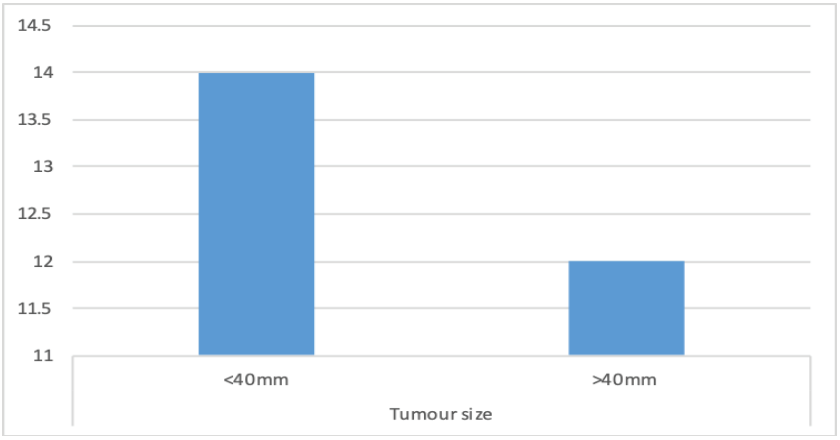

Figure 2 – Number of patients with adrenal masses according tumour size

Non-functional adrenal masses were found in 81%. The frequency of apparent functional tumours (Cushing's syndrome and pheochromocytoma) was 11% (Figure 3). Autonomous cortisol secretion was diagnosed in 22.2%

asymptomatic patients with non-functional adenoma, while in 27.7% they were diagnosed as probable autonomous cortisol secretion (Figure 4).

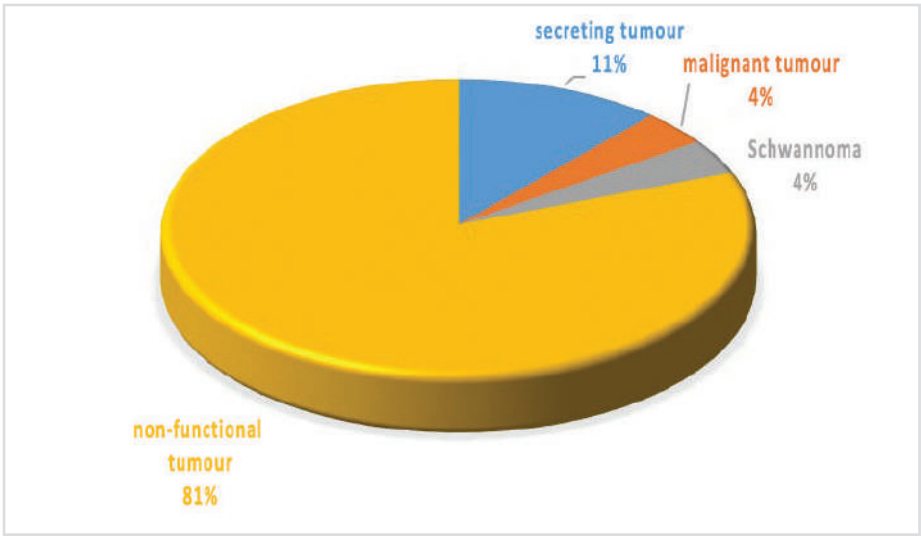

Figure 3 – Type of adrenal tumours

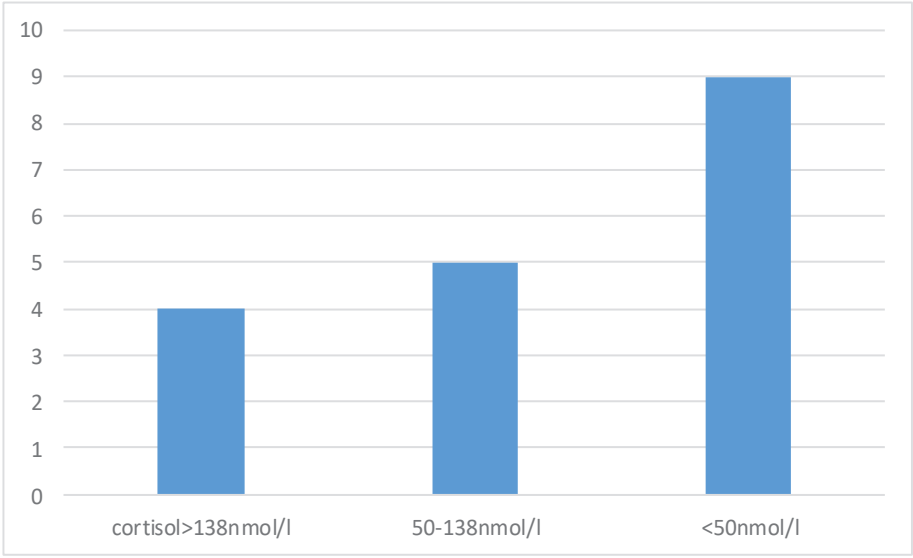

Figure 4 – Number of patients according the results of cortisol after low dose dexamethasone test

One patient (3.8%) had primary adrenocortical carcinoma with the diameter of 8.2 cm, confirmed via radiological characteristics and a histopathologic diagnosis. He died 5 months after surgery from local and distinct metastases.

One young patient (3.8%) had a large tumour 12 cm in diameter with radiological characteristics for adrenal malignant lesion, but histological diagnosis confirmed Schwannoma.

23.06% of the patients with AIs had type 2 diabetes, hypertension in 46.1%, overweigh/obesity in 57%, and other different symptoms in 76% (Table 1).

Statistically significant positive correlation was found between HTA and secreting adrenal tumours ($r=0.426$, $p<0.05$). HTA and age have significant impact on secreting adrenal tumours, as a dependent variable ($p<0.05$) (Table 2).

Table 2

Effect of patients' characteristics on secreting adrenal tumours
Dependent Variable: secreting adrenal tumors

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Model	2,608[a]	9	,290	3,537	,012
age	**,974**	**4**	**,243**	**2,972**	**,049**
sex	,259	1	,259	3,165	,093
Simpt.	,193	1	,193	2,353	,143
DMT2	,145	1	,145	1,774	,200
HTA	**,465**	**1**	**,465**	**5,675**	**,029**
Error	1,392	17	,082		
Total	4,000	26			

a. R Squared = ,652 (Adjusted R Squared = ,468)
Abbreviations:DMT2= diabetes mellitus type 2; HTA= arterial hypertension.

Age, symptoms, and DMT2 have a statistically significant impact on the appearance or prediction of adrenal masses larger than 4 cm ($p<0.05$) (Table 3).

Table 3

Effects of patients' characteristics on tumour size
Dependent Variable: tumour size

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Model	60,103[a]	9	6,678	59,836	,000
age	**3,383**	**4**	**,846**	**7,579**	**,001**
Simpt.	**,883**	**1**	**,883**	**7,908**	**,012**
DMT2	**,681**	**1**	**,681**	**6,103**	**,024**
HTA	,158	1	,158	1,414	,251
sex	,010	1	,010	,091	,766
Error	1,897	17	,112		
Total	62,000	26			

a. R Squared = ,969 (Adjusted R Squared = ,953)

Abbreviations: DMT2= diabetes mellitus type 2; HTA= arterial hypertension.

Of 26 patients, more than a half, 53.8%, underwent surgery, and the others are being followed-up with. The incidence of death within 5 years was 7.7%.

Discussion

Adrenal incidentaloma is a common endocrine disease. The prevalence in autopsy series is 8%, and on CT series more than 4% [1,3,4]. In patients younger than 30 years it is rare, with a prevalence of 0.2%. The prevalence increases with age and it is estimated to be more than 7% in patients of 70 years or older [5].

Regarding demographic characteristics, more AIs were found in patients older than 40 years and the peak of prevalence was above 60 years old. At 60 years old, the patients underwent imaging examinations for others reasons than adrenal diseases.

Furthermore, AIs are found predominantly more in females than in males. This population probably undergoes more physical exams for gastro-intestinal, kidney, and gynaecological diseases.

According to demographic characteristics, the data from a Korean Study, the COAR (Co-work of Adrenal Research), an [9] Italian study, [10] and ours show that the mean age of diagnosis of AIs is 55 years versus 58 and 54.5, respectively. In the Italian study and in ours, masses were commonly found in females, 58.16% versus 61.53%; the median size of tumours (computed tomography measurement) was 3.0 cm (range 0.5 to 25 cm) versus 3.3 cm (range from 1 to 12 cm). We accept a new recommendation [1] for defining AI if it is >1 cm in diameter. In the present study, unilateral lesions were detected in 96.1%, bilateral adrenal masses in 3.8%, and those located on the right side at 52%. Many studies, however, have reported that the left side location is a more frequent finding [11,12].

Evaluation of endocrine status of patients with adrenal incidentaloma is the cornerstone of management [1,5,7,13]. In general, every patient should be screened for glucocorticoid excess, and for adrenal catecholamine and mineralocorticoid excess in selected patients with hypertension and hypokalaemia [14].

Ten to 15% of AIs secreting hormones were in excess. In this study of 26 patients, 81% have non-functional adrenal masses, while 11% were functional; 7.7% were pheochromocytoma and 3.8% was Cushing's syndrome. Patients with symptoms and signs of hypercortisolism should be screened and diagnosed as soon as possible. We found only one patient with Cushing's syndrome who was operated by laparoscopic adrenalectomy. An untreated patient is at high risk for morbidity and mortality [15,16].

Among non-functional AIs asymptomatic patients could be found without the obvious stigmata of Cushing's syndrome, named subclinical Cushing's syndrome or autonomous cortisol secretion [1,7,16]. These patients have hypertension, type 2 diabetes mellitus, obesity, and osteoporosis, as a result of continuous endogenous exposure to cortisol secretion. In our study, autonomous cortisol secretion tumours were at 22.2%, using a 1-mg overnight dexamethasone suppressive test [1], which was performed in 18 out of 26 patients. Four patients with proven autonomous cortisol secretion were at the median age of 45.5 years and the median tumour size was 4.9 cm. We found a statistically significant positive correlation between the level of

cortisol after 1 mg DST and the adrenal tumour size ($r=0.560$, $p<0.05$). Also, there is a statistically significant positive correlation between HTA and secreting adrenal tumours ($r=0.426$, $p<0.05$). These results are supported by other studies that found the cortisol level of post 1- mg DST was an independent cardiovascular risk factor [18,19,20]. This data justifies our decision for surgery. Generally, age, degree of cortisol excess, general health, co-morbidities, and patients' preference should be considered when deciding for surgery [1,7]. Diabetes, hypertension and obesity were improved after surgery; similar data was reported in other studies [5].

Pheochromocytoma is a catecholamine secreting tumour that is found in 5% of adrenal incidentaloma [7,17]. In this study, 7.7% were pheochromocytoma. One patient has a silent pheochromocytoma without hypertension, elevated urinary metanephrine, and a tumour size of 7.7 cm. This was our criteria for surgery. The other young patient (33 years old) has hypertension, with normal urinary metanephrine, and a tumour size of 3.2 cm. Both cases show a different imaging phenotype on CT. Careful examination should be completed. If the results of 24-hour urinary catecholamine metabolites are normal, the measurement of fractionated plasma free metanephrines may be useful. Therefore every patient with AI should be screened for pheochromocytoma, even if the patient is normotensive or asymptomatic before surgery, because silent pheochromocytoma could be lethal [21].

Primary aldosteronism is 1% of adrenal incidentaloma [1]. We did not find any patients with aldosteronoma, but no renin/aldosterone ratio screening was performed since hypokalaemia was not reported in any of the patients.

Primary adrenocortical carcinoma cancer is rare, with an incidence of 1 to 2 cases per 1 million persons [21,22]. In this study, one patient (3.8%) had primary adrenocortical carcinoma with a diameter of 8.2 cm, confirmed on radiological characteristics and histological diagnosis. He died 5 months after surgery from local and distinct metastases. In the cohort of 2005 patients with adrenal incidentalomas, adrenocortical carcinoma was found in 4.7% [7]. The size and imaging characteristics are two major predictors for malignancy [23,24].

Bilateral adrenal masses are found in 15% of the patients with adrenal incidentalomas. In this study, 3.8% were bilateral incidentalomas. Differential diagnosis includes bilateral metastases, bilateral incidentaloma, congenital adrenal hyperplasia or infiltrative lesions. Patient follow-up is recommended, as it is in unilateral adrenal incidentaloma. If one of the adrenal masses grows more than 20% from the initial radiological measurement, surgery is indicated [7,25].

CT is used at the initial diagnosis in patients with adrenal masses. It is a useful tool in distinguishing benign from malignant lesions, but not the functionality of the tumour. In all AIs, a non-contrast (unenhanced) CT is recommended as the first line of investigation with the determination of HU. An adenoma with <10 HU is consistent in lipid-rich benign adenoma. A contrast-enhanced washout CT may be used as the next test for characterizing the adrenal incidentaloma. CT characteristics and tumour size were used in all patients in our study, as part of the strategy for surgery or follow-up.

According to European and other recommendations, surgical treatment is necessary in selected patients [1, 14, 25]. Laparoscopic adrenalectomy is the first line of treatment for patients with AI [26, 27]. In our study, 53.8% of patients underwent surgery, by an expert surgeon. The histopathological findings were: 3 functional adenoma, 3 autonomous cortical secretion, 1 adrenocortical carcinoma, 3 cysts, 1 Schwannoma, and 3 adrenocortical adenomas.

About 46.2% of patients are sent for follow-up, without evidence of growth of the tumour or hyperfunctioning.

Conclusion

In this small study of 26 cases with adrenal incidentalomas, 11.5% were benign hypersecreting tumours and there was only one patient (3.8%) with a malignant tumour. Appearance of symptoms, age, or tumour masses larger than 4 cm are more likely to be secreting or malignant tumours. A lifelong follow-up for patients is needed in order to establish undiscovered cases of malignant or hypersecreting tumours among non-operated patients.

No potential conflict of interest relevant to this article was reported.

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Бранкица КРСТЕВСКА, Живко ПОПОВ

ДИЈАГНОЗА И МЕНАЏМЕНТ НА ПАЦИЕНТИ СО АДРЕНАЛНИ ИНЦИДЕНТАЛОМИ: НАШИ ИСКУСТВА

Резиме

Вовед. Инциденталомите на надбубрежните жлезди (АИ) се случајно откриени надбубрежни маси со имиџиг техниките. Тие се нефункционални или функционални, бенигни или малигни лезии.

Цел. Презентирање на 5-годишно искуство со дијагностицирање и следење на надбубрежните инциденталоми, со посебен акцент на нивната хормонална активност и диференцијација на бенигни од малигни маси.

Материјал и методи. Група од 26 пациенти беа вклучени во оваа ретроспективна студија спроведена во Центарот по интерна медицина „Срце“. Кај сите пациенти е извршен клинички преглед, КТ и хормонални тестови.

Резултати. Од 26 пациенти (10 мажи и 16 жени), на просечна возраст од 54,5 (опсег, од 25 до 80) години, со просечна големина на туморот од 33 mm, едностранн беа 96,1 %, и тоа на десната страна во 52 % од случаите. 96 % беа бенигни маси, од кои 81 % беа несекретирачки тумори. Нефункционална асимптоматска автономна секреција на кортизол имаше кај 22,2 %, 7,7% беа феохромоцитоми, 3,8 %

Кушингов синдром, адренокортикален карцином во 3,8 % и Шванома во 3,8 %. Пронајдена беше статистички значајна позитивна корелација помеѓу ХТА и секреторните надбубрежни тумори ($r = 0,426$, $p < 0,05$) и помеѓу пост-супресивното ниво на кортизол и големината на надбубрежниот тумор ($r = 0,560$, $p < 0,05$). Возраста, симптомите и DMT2 имаат статистички значително влијание на појавата на туморските маси поголеми од 4 см ($p < 0,05$). 53,8 % од пациентите беа оперирани, а другите се следеа.

Заклучок. Во оваа мала студија со 26 случаи со надбубрежни инцидентоломи, 11,5 % биле бенигни хиперсекретирачки тумори, а само еден пациент (3,8 %) имаше малиген тумор. Присуството на симптоми, возраста или туморски маси поголеми од 4 см имаат поголема веројатност да бидат сектеритачки или малигни тумори.

Клучни зборови: надбубрежни инциденталоми, феохромоцитом, „автономна секреција на кортизол“, големина на тумор.