Clinical and radiological characteristics of functional adrenal tumors

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GRADUATE THESIS

Zagreb, 2019

This graduate thesis was made at the Department of Endocrinology, University Hospital Centre Zagreb, mentored by doc. dr. sc. Tina Dušek and was submitted for evaluation in the academic year 2018/2019.

Abbreviations

ACC	Adrenocortical carcinoma
ACTH	Adrenocorticotropic hormone
APA	Aldosterone-producing adenoma
ARR	Aldosterone-to-renin ratio
AVS	Adrenal venous sampling
BAH	Bilateral adrenal hyperplasia
BP	Blood pressure
CLR	Contralateral suppression ratio
CS	Cushing syndrome
CT	Computed tomography
DHEAS	Dehydroepiandrosterone sulfate
DRC	Direct renin concentration
DM	Diabetes mellitus
ENSAT	European Network for The Study of Adrenal Tumors
ESE	European Society of Endocrinology
HU	Hounsfield units
IVC	Inferior vena cava
MRI	Magnetic resonance imaging
ONDST	Overnight dexamethasone suppression test
PASAT	Pure androgen secreting adrenal tumors
PHD	Pathohistological diagnosis
PHEO	Pheochromocytoma
PA	Primary hyperaldosteronism
PRA	Plasma renin activity
RAS	Renin-angiotensin system
SCS	Subclinical Cushing syndrome
SIT	Saline infusion test
SLT	Salt loading test
UFC	Urine free cortisol

Summary

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Objective: To perform statistical analysis of the radiological findings of adrenal gland tumors found in patients referred to the department of endocrinology in the University Hospital Center Zagreb between the years of 2011-2016. With the aim of improving the diagnosis process, such patients need to go through.

Methods: The patients utilized in this study accounted for the KBC Zagreb patient registry. The data was then analyzed via an Excel database and manifested into a conclusion. Literature used in this study was found using Medline via the MeSH search engine using the same keywords listed below.

Results: Data on tumors include adenomas, PHEO and ACC. In our study the size of adrenal tumors classified as an adenoma on radiological testing ranged from 0.9 to 7.4 cm with an average of 3.95 cm; conversely, the diameter of ACCs ranged from 1.2 to 17.4 cm with an average of 10.1 cm. Additionally, in the results of our study 96% of PHD proven PHEO had non-adenoma radiological characteristics and the average size of these tumors was 6.3 cm.

More so, among tumors that were larger than 4 cm and with radiological characteristics of a non-adenoma tumor, the prevalence of malignant tumors was 61 percent and of benign tumors was 38%.

Conclusion: Our study thus supports the hypothesis that tumor size and attenuation value greater than 10 HU on CT is correlated with malignancy potential of adrenal gland tumor. Furthermore, in order to optimize the accuracy of diagnostic testing for the work-up of adrenal gland masses, PHD should remain the preferred method.

Key words: Adenoma, Non-adenoma, Cushing syndrome, Autonomous cortisol secretion, Pheochromocytoma, Hyperandrogenism, Primary aldosteronism

Sažetak

Naslov: Kliničke i radiološke karakteristike funkcionalnih tumora nadbubrežne žlijezde

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Cilj: Za statističku analizu radioloških nalaza tumora nadbubrežne žlijezde pronađenih kod pacijenata upućenih na Zavod za endokrinologiju KBC-a Zagreb u razdoblju od 2011. do 2016. godine. U cilju poboljšanja dijagnostičkog procesa kroz kojeg takvi pacijenti moraju proći.

Metode: Podaci o pacijentima korišteni u ovoj studiji su preuzeti iz registra pacijenata KBC Zagreb te su analizirani putem Excelove baze podataka i prikazani u zaključku. Literatura korištena u ovom istraživanju pronađena je na Medline-u putem MeSH tražilice korištenjem istih ključnih riječi navedenih u nastavku.

Rezultati: Podaci o tumorima uključuju adenome, feokromocitome i adrenokortikalne karcinome. U našem istraživanju veličina tumora nadbubrežne žlijezde klasificiranih kao adenom na radiološkom ispitivanju kretala se od 0,9 do 7,4 cm s prosjekom od 3,95 cm. Suprotno tom, promjer adrenokortikalnih karcinoma kretao se u rasponu od 1,2 do 17,4 cm s prosjekom od 10,1 cm. Osim toga, u rezultatima našeg istraživanja 96% PHD dokazanih feokromocitoma imalo je radiološke karakteristike neadenomskih tumora, a prosječna veličina tih tumora bila je 6,3 cm. Štoviše, među tumorima većim od 4 cm i s neadenomskim radiološkim karakteristikama, učestalost malignih tumora bila je 61%, a benignih tumora 38%.

Zaključak: Naša studija stoga podupire hipotezu da je veličina tumora i vrijednost prigušenja veća od 10 HU na CT-u u korelaciji s malignim potencijalom tumora nadbubrežne žlijezde. Nadalje, kako bi se optimizirala točnost dijagnostičkih ispitivanja za obradu nadbubrežnih masa, PHD bi trebala ostati preferencijalna metoda.

Ključne riječi: Adenom, Neadenom, Cushingov sindrom, Autonomno izlučivanje kortizola, Feokromocitom, Hiperandrogenizam, Primarni aldosteronizam

1. **Preface**

Adrenal tumors classification

Adrenal masses are commonly subdivided into adenomas and non-adenoma tumors.

Adenomas are benign tumors that may be non-functioning or hyper-functioning with the secretion of one, or a combination of the following hormones: cortisol, aldosterone and androgen.

Non-adenomas are a malignant tumor that are similar to adenomas and may be non-functioning or hyper-functioning. The most frequently diagnosed non-adenoma tumors are: pheochromocytoma (PHEO), adrenocortical carcinoma (ACC), metastasis and myelolipoma [1].

Furthermore, in order to distinguish between adenomas and non-adenoma tumors, the current recommendation is to use Computed Tomography (CT) attenuation values, expressed in HU. The cutoff value is 10 HU, with less or equal to 10 indicating an adenoma and higher than 10 demonstrating a non-adenoma. The cutoff value for diagnosis is 4cm in diameter; if a mass is equal to or larger than this it is likely malignant whereas a mass smaller than this is likely benign. [2]

Cushing Syndrome

Cushing Syndrome (CS) is caused by exposure to excessive cortisol, which may be exogenous or endogenous. Endogenous CS is an uncommon manifestation with an incidence rate of 0.7-2.4 cases per million people per year[3]. Endogenous CS is commonly classified as; adrenocorticotropic hormone (ACTH) dependent and ACTH independent. The prevalence of ACTH independent CS accounts for 15-20% of all endogenous CS cases. Additionally 90% of these cases are attributed to being a unilateral adrenal tumor and approximately 80% of these tumors are adenomas, while the rest are ACC[4].

The signs and symptoms of CS are variable, with weight gain being the most common presenting symptom. In addition, other clinical features of cortisol hyper-secretion include facial plethora, buffalo hump, moon face, violaceous striae, bone disease, psychiatric disturbances and cognitive impairment[5,6]. The diagnosis and treatment of CS is important since there is a high morbidity and mortality associated with untreated

CS. CS is associated with an increase in metabolic and cardiovascular pathological states that may not return to complete normalization even with treatment, thus early recognition of CS is crucial [7].

The recommended biochemical testing for the diagnosis of CS is to perform one of the following tests: 2 measurements of 24-hour urine free cortisol (UFC) 2 measurements of late-night salivary cortisol testing, and at least two measurements of the 1-mg overnight dexamethasone suppression test (ONDST). In the case that the results of these tests suggest cortisol hypersecretion, the next diagnostic step is to measure the levels of ACTH to distinguish between ACTH dependent CS or ACTH independent CS [8]. Low levels of ACTH indicate an ACTH independent CS variant and thus adrenal imaging should be done. CT is the recommended radiological method due to its high specificity in the differentiation between an adrenal hyper-functioning adenoma and an adrenal hyper-functioning non-adenoma[3].

The treatment of CS is via surgical resection of the hyper-functioning tumor. For patients who cannot undergo surgery, medical therapy allows for the reduction of hormone production and the effect that excess cortisol is causes[4].

Autonomous cortisol secretion

Subclinical Cushing Syndrome (SCS) is the autonomous secretion of cortisol from an adrenal adenoma independent of ACTH, in congruence with the lack of an overt cushingoid phenotype[9]. The term SCS has recently been changed to "autonomous cortisol secretion" (ACS). The prevalence of ACS accounts for15-20% of patients with adrenal incidentalomas(AI)[10].

Most of adrenal AI cases do not evolve into full CS symptoms and are limited to only laboratory abnormalities[11]. In patients with ACS the occurrence of obesity, hypertension, glucose metabolism disorders and bone alterations are higher than when compared to matched controls[12]. In order to decrease the incidence of cardiovascular events and metabolic bone disease in these patients, the appropriate diagnosis and treatment of ACS is crucial.

More so, ACS is enigmatic and may be misdiagnosed as poor life style habits, metabolic syndrome, diabetes mellitus (DM) or essential hypertension[12].

For the diagnosis of ACS it is recommended to use the 1 mg overnight dexamethasone suppression test (ONDST) as the initial screening test, with a cortisol level of greater than 50 nmol/L being indicative of autonomous cortisol secretion disease[2]. However, due to the high nature of false positives results from obesity, DM, depression, alcohol dependence, inductors of P450 3A4 and adulterated cortisol binding globulins, an additional confirmatory test is recommended[9]. One of the confirmatory tests that can be performed is the late-night salivary cortisol (LNSC) level, which is considered positive when serum cortisol levels are greater than 150 nmol/L. Another confirmatory test is the 24 hour urine free cortisol (UFC) level, with levels higher than 124nmol/24h being considered a positive result[11]. However, this test also has a low sensitivity accompanied by discrete false positive and false negative values that limit its utility in diagnosing SCS. The disadvantages of this test mainly derive from the inconvenience and inaccuracies of testing, as one measuring error can potentially adulterate the entire procedure[11]. Additionally, measurement of ACTH levels offer insight to the pathology, since serum levels of ACTH are usually found to be higher in ACS patients in comparison to patients with evident CS[12].

There isn't a consensus in literature regarding the management of ACS. There is a choice between undergoing surgery and removing the adrenal mass or conservative medical treatment. Thus, the recommended approach is to have a personalized treatment plan for every patient. Surgery is commonly offered to younger patients and patients with comorbidities likely due to cortisol excess such as DM 2, hypertension and bone disorders that are not well controlled[2,10].

Pheochromocytoma

Pheochromocytoma (PHEO) is a non-adenoma tumor that arises in the adrenal medulla and secrete catecholamines. They may be non-functioning or hyper-functioning. The size of a PHEO is inversely related to its hyper-secretory potential[13]. Additionally, PHEO can be either a benign or a malignant tumor, with the prevalence of malignant PHEO being approximately 10%[14]. PHEO is found in around 8% of patients with an AI[15]. Indeed, PHEO is found in 0.05-0.2% of patients with hypertension[16]. Furthermore, 10% of patients diagnosed with PHEO are asymptomatic[17]. The majority of PHEO are sporadic and around 25% of patients with PHEO have a genetic predisposition due to a germline mutation[18].

The classic symptoms of PHEO are headache, diaphoresis, palpitations tachycardia and sustained or paroxysmal hypertension[19]. Glodny et al. found that the characteristic signs of PHEO mentioned above are more commonly found in patients with a benign tumor, perhaps explaining why malignant PHEO suffer from a delayed diagnosis that is corollary to the dismal prognosis[20].

CT attenuation values remain a reliable method for distinguishing between an adenoma and a non-adenoma tumor of the adrenal gland. A CT attenuation value of 10 Hounsfield units (HU) is the cutoff value for diagnosis, with less than 10 HU suggesting an adenoma and above 10 HU being indicative of a non-adenoma, such as PHEO[2].

There are no reliable histological features that can definitively differentiate between malignant and benign PHEO; thus all patients with PHEO tumors should undergo surgery and have the mass resected[21].

All patients with an AI or those who present with the signs and symptoms of PHEO should have hormonal testing to measure if their plasma-free metanephrines or urinary fractionated metanephrines are above the cut-off values for the diagnosis of PHEO. In cases of which the CT attenuation of the adrenal tumor is below or equal to 10 HU, hormonal testing is not required due to the low distribution of PHEO that have a HU attenuation value less than 10[2,22].

Hyperandrogenism

Pure androgen secreting adrenal tumors (PASAT) are extremely rare. Moreno et al. described only 21 cases of women diagnosed with PASAT over a range of 33 years. He reported that out of the 801 adrenalectomies performed, only 2.4% were due to PASAT[23]. Cordera et al. reported a similar finding in which over a period of 50 years, only 11 female patients with PASAT were operated on at Mayo Clinic[24].

In regards to symptomatology of PASAT, the most common findings are hirsutism, virilization syndrome and disruption of the normal menstrual cycle[24].

The mean size of PASAT varies according to whether it is a benign or a malignant tumor. Both Cordera and Moreno et al demonstrated that a malignant tumor tends to be larger than a benign tumor. The former presenting the mean diameter for a benign PASAT as 4.2 cm and for malignant tumors as 9.8 cm. Moreno and cohort found that

benign tumors had a mean diameter of 9cm and malignant tumors had a mean of 14cm[24,23].

Since both ovarian tumors and adrenal tumors can cause virilization due to excess secretion of androgens, it is important to identify the correct location of the tumor prior to surgery. One method described to differentiate the two tumors is 'dynamic hormonal tests' which involves stimulating or suppressing hormone secretion. However they are unreliable and thus the best method is to use radiologic methods such as CT, MRI or adrenal venous sampling(AVS)[24,25,26].

In addition, the measurement of the major androgens can help distinguish if the hormonal excess originates from the ovary or adrenal gland.

High testosterone levels in a woman with virilization is commonly indicative of an ovarian tumor[26]. Whereas, dehydroepiandrosterone sulfate (DHEAS) is the best marker for PASAT[23].

Resection via surgery is the recommended treatment for these tumors. A laparoscopic adrenalectomy is recommended in cases in which the tumor is less than 6 cm in diameter and assumed to be benign. On the contrary, an adrenalectomy via an open anterior transperitoneal approach is suggested in the case of a malignant tumor[24].

Primary Aldosteronism

Primary aldosteronism (PA) was first described in 1953 by Michał Lityński, a Polish internist[27]. Later on in 1955, Dr. Jerome W. Conn went on to describe the three major findings that depict the diagnosis of PA including hypertension, suppressed plasma renin activity (PRA), and increased aldosterone excretion[28].

The incidence of PA varies among literature reports. A meta-analysis done by Kayser et al. found that in hypertensive patients, the prevalence of PA was 3.2%-12.7% in primary care institutions and 1%- 29.8% in referral centers[29].

Furthermore, in patients suffering from treatment resistant hypertension (defined as blood pressure (BP) >140/90 mm Hg despite a three drug regimen, including a diuretic) the prevalence of PA is seen in up to 20%[30,31].

The common causes of PA are an Aldosterone-producing adenoma (APA), and unilateral or bilateral adrenal hyperplasia (BAH). The rare cases of PA are usually due to adrenal carcinoma or from inherited conditions of familial hyperaldosteronism[32].

It is very important to have an early diagnosis of PA in order to decrease the risk of suffering from comorbidities associated with it. Patients with PA have an increased risk of cardiovascular and cerebrovascular events with damage to the heart and kidney compared to patients diagnosed with essential hypertension. There is also an increased prevalence of metabolic syndrome and diabetes, along with signs and symptoms of depression and an overall decrease in the quality of life[33].

In 2016, the European Society of Endocrinology (ESE) together with the European Network for the Study of Adrenal Tumors (ENSAT) published guidelines regarding the management of PA. They recommended to test for PA in high risk groups. For example; patients with sustained BP above 150/100 mmHg on three measurements obtained on different days, patients with treatment resistant hypertension, patients suffering from hypertension along with spontaneous or hypokalemia caused by a diuretic, patients with hypertension and a diagnosed AI[32].

It is important to notice that the above groups are mainly considered to be high risk due to the presence of hypertension in their medical status without consideration for the presence of hypokalemia, since this is only found in 28% of patients with due to a renal potassium wasting phenomena PA[34,35,36].

For the diagnosis of the PA, it is acceptable to follow a three-step algorithm.

- Firstly, the plasma aldosterone concentrations (PAC) and plasma renin activity (PRA) or direct renin concentration (DRC) is measured. It is considered positive if PAC is ≥ 277 pmol/L and PRA is less than 1.0 ng mL^{-1} h^{-1} or DRC is below the reference range. Before checking the above concentrations, patients should follow a low salt diet and be restricted to a minimum intake of only 5 g NaCl/day. If suffering from hypokalemia, the electrolyte disturbance should be corrected prior to testing. In addition, it is recommended that blood samples are taken in the morning and after patients are out of bed for at least two hours[33].
- Secondly, patients that have a positive screening test should continue to have at least one or more confirmatory tests to prove the autonomous secretion of aldosterone with aldosterone suppression testing. Confirmatory testing is not considered necessary when the diagnosis is obviously PA from the lab results showing spontaneous hypokalemia with PAC >20 ng dL (550 pmol/L) and with PRA (or DRC) below assay detection[32].

The most commonly used aldosterone-suppression tests are saline loading. This is either done by using an IV saline infusion test (SIT) and then measuring of the PAC (cut-off values of PAC are > 5–10 ng/dL (140–280 pmol/L) or an oral salt loading test (SLT) with measurement of urine aldosterone (uAldo), with a cut off value of uAldo > 12 μg/24 h (33 nmol/day) or >14 μg/24 h (39 nmol/24 h)[32,33]. Other less commonly used tests are the fludrocortisone suppression test and captopril challenge test[37].

- Lastly, patients who are positive for having PA according to the above confirmatory tests should continue with subtype testing. This is done with a CT scan in order to exclude the presence of an aldosterone secreting carcinoma. However, the current imaging techniques often lack the ability to display the exact location of the source of aldosterone excess, and micro-APAs (≤10 mm in diameter) are frequently not seen by CT or MRI. In addition, with the increase in the amount of diagnosed AI, there is an increase in false positive results and a reduction in the specificity of this imaging test[33]. Thus, it is highly recommended that in addition to a radiological test, an AVS is also done in every patient diagnosed with PA who is suitable to go for surgery in order to distinguish an unilateral from bilateral PA[32].

  However, in the rare case of a young patient (<35 years) who on imaging has the finding of a unilateral adenoma (>10 mm together with a normal contralateral gland), and severe PA (e.g. spontaneous hypokalemia and PAC > 30 ng/dL) a unilateral adrenalectomy would be the recommended approach and obviate the need for AVS[32,38,39].

The optimal time to perform the AVS procedure is in the morning while fasting and to have the patient in a supine position for at least an hour before sampling, since the ACTH-stimulated aldosterone production would be at its peak during this period and to also avoid the effects that postural changes have on the stimulation of the renin–angiotensin system (RAS).

In addition, all antihypertensive drugs that affect the RAS axis, should be discontinued for four weeks prior to the procedure. If however, antihypertensive drugs are still required in this period of time the use of medications that have a lower effect on the RAS should be used (For example; alpha 1-adrenergic receptor blockers and non-dihydropyridine long-acting calcium channel blockers[32].

The procedure begins with the administration of a cosyntropin infusion or bolus. This is done to both minimize the stress induced fluctuations in aldosterone secretion and to also maximize the gradient of cortisol from the adrenal vein to inferior vena cava, which is an indicator of a successful sampling of the adrenal vein[40].

In the procedure there are three important indexes to be calculated in order to have conformation that the procedure was successfully performed and to have the right diagnosis.

The three indexes are the following:[33,41,42]

1) Selectivity index: cortisol from adrenal vein/ cortisol from the peripheral vein (commonly the Inferior vena cava, IVC).

   If the ratio is ≥5 on each side, the cannulation of the adrenal veins was Successful.

2) Lateralization index: aldosterone/cortisol ratio from high Concentration to low concentration

   A ratio of more than 4:1 indicates unilateral aldosterone excess. A ratio of less than 3:1 suggests bilateral aldosterone hypersecretion.

3) Contralateral suppression ratio (CLR): aldosterone/ cortisol ratio from the low side to the IVC.

   It is used to determine if the aldosterone production is suppressed in the non-dominant gland. (CLR ≤ 1 indicated suppression)

The use of AVS to localize the APA is strengthened by numerous studies that prove that AVS is superior to CT or MRI, both of which lack sensitivity and specificity in localizing the APA[43,44,45]. However, there is a contention of whether AVS should be considered the gold standard procedure in defining the subtype of PA. The two main issues around this debate is that the recent Spartacus Trial showed that in the treatment of PA, on the basis of CT findings compared to AVS findings, there were no significant differences in clinical outcomes for patients who were followed for a period of one year[46]. Also in order to successfully perform an AVS, There is a certain level of expertise and experience necessary to successfully complete the test and thus is recommended to have a radiologist supervise the procedure in order to maximize success rates. [37,47]. This level of expertise is commonly found in highly specialized

referral centers, obviating the availability of the procedure to all patients that are not treated in such centers.

The treatment of PA differs according to the findings seen on the AVS. In a case of unilateral PA, the best possible treatment in order to achieve clinical improvement is an adrenalectomy. Patients with a bilateral PA or with a unilateral PA not undergoing surgery is handled with medical treatment, namely a mineralocorticoid antagonist[32].

2. Hypothesis

With the premise in mind that malignant and benign adrenal tumors have distinctive features which would allow us to further characterize and allow discernment from a clinical standpoint, we postulate that such tumors can be diagnosed as benign or malignant based on radiological and histological diagnostic findings. Furthermore we believe that certain tumors are more likely to be benign or malignant than other subtypes based on statistical analysis of their morphology and seek to verify this supposition based on real patient data obtained via diagnostic testing collected at the clinical hospital Zagreb.

3. Objective

To perform a statistical analysis of radiological findings of adrenal gland tumors. By defining what is the average size of specific tumors and the likelihood of a specific tumor to be an adenoma or a non-adenoma, we may offer a better diagnostic approach to patients that are referred to our clinic with adrenal tumors. This will reduce the amount of unnecessary testing done on patients and thus be cost effective and will lower the emotional burden on patients that are waiting for results and further testing.

4. Material and Methods

Patients

The study was comprised of 105 patients, 33 (31%) were males and 72 (69%) were females with a mean age of 52 years (range, 24-75 years) that were referred to the Department of Endocrinology, University Hospital Zagreb, between the years of 2011-2016. These patients were referred to the department following the finding of a functional adrenal tumor. All patients had hormonal assays and a CT scan performed in order to conclude if the tumors were an adenoma or a non-adenoma and if it was non-functioning or hyper-functioning

Methods

In this study we looked at patients that were diagnosed with a hyper-functional adrenal tumor on the ground of their hormonal assay results.
The hyper-functioning tumors that were diagnosed are; PHEO, PA, CS and ACS.

Imaging studies

The adrenal masses were further divided into adenoma and non-adenoma tumor according to the radiological findings on CT by measuring the HU.

Statistical analysis

This was a retrospective study in which we reviewed the medical records at our department of patients diagnosed with an adrenal tumor. Descriptive information of the baseline characteristics of patients was gathered and summarized in Excel. We further analyzed this information in Excel, which is displayed in our study as frequencies (percentages) for categorical variables and mean (ranges) for continuous variables.

Literature Search

The literature used for the purpose of this thesis was found by utilizing the medline database, specifically by using the MeSH search engine function. Keywords used in the MeSH search included: adrenal tumors, adenoma, Cushing syndrome, primary aldosteronisim, subclinical Cushing syndrome, and pheochromocytoma. Literature was also found by using the references of selected journal articles and books that were used in the original text.

5. Results

Table 1 Demographic Characteristics and Histopathological Results

Age at diagnosis [mean range (y)]		52 (24-75)
Sex	**Female, N (%)**	72 (69)
	Male, N (%)	33 (31)
Adenoma (%) (N=57)		54
ACC (%) (N=12)		11
PHEO (%) (N=27)		26
ACC; adrenocortical carcinoma; PHEO; pheochromocytoma		

From the results of table 1, we see that the mean age at diagnosis of the patients in our study is 52 years. Seventy two percent of the participants are females. The distribution of the different types of adrenal tumors analyzed according to PHD findings is 54% as adenomas, with 11% being ACC and 26% as PHEO.

Table 2 Size and radiological characteristics of tumors with respect to their PHD findings

	Tumor size [mean range (mm)]	**Tumors with non-adenoma radiological characteristics (%)**
Adenoma (N=57)	39.5 (9-74)	39
ACC (N=12)	101 (12-174)	67
PHEO (N=27)	63 (25-120)	96
ACC; adrenocortical carcinoma; PHEO; pheochromocytoma		

Table 2 shows the mean size of the tumors, as was seen on CT. We further analyzed for proven adenoma, ACC & PHEO on PHD what was the percentage of tumors that were characterized as non-adenoma type of tumor on CT. The results show that 39 % of adenomas, 67 % of ACC and 96 % of PHEO were characterized as a non-adenoma type of tumor on CT. In addition, the mean size of adenoma was 39.5 mm, ACC was 101 mm and PHEO was 63 mm.

Table 3 Size of adenomas with respect to their functional phenotype

	Tumor Size [mean range (mm)]	**Tumors with non-adenoma radiological characteristics (%)**
Cushing Syndrome (N=19)	51 (12-156)	58
Autonomous Cortisol Secretion (N=11)	52 (17-174)	45
Primary Hyperaldosteronism (N=42)	32 (9-75)	27

The analysis of table 3 shows the mean size of the different types of adrenal adenomas with respect to their functional phenotype. In addition, we can see the percentage of tumors that were classified as non- adenoma from radiological imaging. The mean size of adenomas in patients with CS was 51 mm and 58% of these tumors were classified as non- adenomas on CT. The mean size of adenomas in patients with ACS was 52 mm and 45% of these tumors were classified as non- adenomas on CT. The mean size of adenomas in patients with PA was 32 mm and 27% of these tumors were classified as non- adenomas on CT.

Table 4 Size and Radiological Characteristics of PHD proven adenoma

Unenhanced CT attenuation (HU category)	**Tumor Size [mean range (mm)]**
≤ 10 HU (N=34)	36 (33-70)
> 10 HU (N=23)	45 (9-74)

The analysis of table 4 is of diagnosed adenomas based on PHD (N=57). The mean size of these tumors that were ≤10 HU on CT was 36 mm. The mean size of tumors that were ≥10 HU on CT was 45 mm.

Table 5 The prevalence of benign and malignant tumors among the tumors with a size > 4 cm and with non-adenoma radiological characteristics

Tumor Type	**%**
Benign (N=20)	38
Malignant (N=32)	61

The analysis of table 5 shows the percentage of tumors that were classified as a benign or a malignant type of tumor according to PHD among the tumors that had a size greater than 4 cm and with non-adenoma characteristics on CT. The percentage of benign tumors was 38% and the percentage of malignant tumors was 61%. Furthermore, the tumors classified as benign were either an adenoma (N= 14), cyst (N=1), adrenal myelolipoma (N=2), oncocytoma (N=1) or hyperplasia (N=2). In addition, the tumors classified as malignant were ACC (N= 8), PHEO (N=22), hemangioma (N=1), paraganglioma (N=1).

Table 6 Radiological characteristics of tumors with respect to their malignancy correlation

	Tumors with adenoma radiological characteristics (N=41)	**Tumors with non-adenoma radiological characteristics (N= 64)**
Benign tumor distribution	90%	42%
Malignant tumor distribution	10%	58%

Table 6 shows the correlation between the radiological characteristics of tumors with their pathohistological finding being a benign or a malignant tumor. The percentage of tumors that were classified as an adenoma according to CT findings and further diagnosed as a benign tumor was 90%, while the rest were a malignant tumor. Additionally, the percentage of tumors that were classified as a non- adenoma according to CT findings and further diagnosed as a benign tumor or a malignant tumor was 42% and 58% respectfully.

6. Discussion

When an adrenal tumor is diagnosed it is important to correctly identify it as an adenoma or a non-adenoma tumor and whether it is hyper-functioning or a non-functioning tumor. The preferred method to monitor the functioning potential of a tumor is with the use of biochemical testing. In order to differentiate an adenoma from a non-adenoma and a malignant tumor from a benign one, the size of the tumor together with the attenuation values on CT expressed in HU is used. However, many studies throughout the literature have shown that the use of attenuation values on unenhanced CT scan is superior to the utilizing the size of the tumor[48,49,50]. Lee et al. independently utilizing a size cutoff value of 2.5 cm as an unbiased factor in differentiating benign from malignant tumor had an adequate sensitivity of 84%, however the specificity of 79% was insufficient[48]. In his study of over 1000 patients, Mantero et al. found that there is a sensitivity of 93% when the cut off value of 4 cm is used in order to distinguish

benign from malignant tumors[51]. In addition, in 2002 NIH recommendation's concerning the work-up of AI, essentially stated to observe and monitor tumors that are less than 4 cm since almost all of these lesions are benign[52]. In 2016 ESE together with ENSAT published guidelines regarding AI. In these guidelines, tumors that are less than 4 cm in size together with less than 10 HU with features characteristic of a benign tumor on CT, need no additional imaging on follow up [2]. Furthermore, in tumors that are greater than 6 cm in size, the ratio of benign to malignant is approximately 1:8 which indicates the necessity to surgically remove these masses due to the increased malignant potential[53]. Our study showed that the diameter of adrenal tumors classified as an adenoma on radiological testing ranged from 0.9 to 7.4 cm with an average of 3.95 cm; conversely the diameter of ACC tumors ranged from 1.2-17.4 cm with an average of 10.1 cm. These findings are consistent with the values reported in literature that often cite a cutoff value of 4 cm when distinguishing between a benign or malignant adrenal tumor. Indeed, while the guidelines would not have caught smaller ACC tumors such as 1.2 cm in our cohort. An average size of 10.1 cm suggests some efficacy of using these size recommendations in the treatment of adrenal gland tumors.

In our study, we used the cut off value of 10 HU among other things in order to distinguish between an adenoma and a non- adenoma. With below 10 HU indicating an adenoma and above 10 HU representing a non-adenoma. The vast majority of PHEO shows attenuation values of more than 10 HU[2,22]. The results of our study which showed that 96% of PHEO had non-adenoma radiological characteristics are supported by previous reports in literature. The remaining 4% of patients would remain undiagnosed by the use of attenuation values alone, however they could have been diagnosed based on the size of the tumor as the PHEO had an average size of 6.3 cm.

Young et al. showed that 60% of PA is due to bilateral idiopathic hyperplasia (IHA), 30% are due to APA and less than 1% are due to aldosterone producing ACC. Our results regarding PA displayed that 27% showed non-adenoma characteristics according to findings on CT. The PHD of such tumors showed that out of 11 tumors with PA, only 1 (9%) was ACC and 10 (91%) were adenomas. Interestingly, the discrepancy shown in the results between radiological and PHD findings indicate a certain level of false positive results. The ramifications of this could be that more invasive unnecessary testing are taken.

The prevalence of malignant tumors among tumors that were larger than 4 cm and with radiological characteristics of a non-adenoma tumor was 61 percent. Thus, showing that both large size tumors and higher unenhanced CT attenuation have increased synergistic accuracy when used together compared to each of them separately. In addition, tumors that had radiological characteristics of an adenoma were proven by PHD to be a benign type of tumor in 90 percent of cases. Indicating that these new radiological recommendations have a sensitivity of 90% for detecting malignancy. Therefore, due to potentially missing 10% of diagnosis, radiology should not be the sole test for detection. While 58% of tumors with radiological characteristics of a non-adenoma were proven by PHD to be a malignant type of tumor. This indicates a high degree of accuracy in regards to the former situation, whilst in the latter, due to the risk of not properly diagnosing a malignant tumor, clinical setting should guide us in the management of patients.

Based on the findings of this study and the conclusions made by other reports in literature, our results showed that using the size and radiological characteristics of a tumor show modest efficacy in diagnosing benign adenomas. Therefore our results support the notion of using both of these parameters along with each patient's individual situation and presentation for the diagnosis and treatment of adrenal tumors.

Limitations of this study are a limited sample size which would affect numerous parameters including the average size of tumors with their correlated diagnosis, as well as the sensitivity of using radiological and histological testing as a diagnostic tool. Other sources of error in this study could have arisen from the innate user error that accompanies using radiological and histological testing.

7. Conclusion

Throughout the course of this study, the quantitative analysis of our patient population and review of literature showed that indeed our hypothesis was correct. The increasing size of the tumor correlates with its probability of being a non-adenoma type of tumor. In addition, when studying the efficacy of radiological versus histological methods of diagnosis, the prevalence of tumors classified as a non-adenoma on CT and further proven on PHD to be a non-adenoma was 67% and 96% for ACC and PHEO, respectively. Thus, PHD was proved to be far more accurate in the ability to deliver a diagnosis. While this is very promising for the characterization and workup of adrenal tumors, thus study is still in the nascent stages and further studies and examinations should be pursued in order to obtain a more concrete supposition.

Acknowledgments

I would like to thank my mentor, Dr. Tina Dušek with whom I had the pleasure to work with and receive guidance and vast knowledge.

I would also like to thank my parents, grandparents and my entire family for all their support throughout this journey and for making it possible for me to pursue my dream.

A very special thank you is to my dear husband that has taught me so much about life, love and happiness. Your endless support through all the good times and the bad allow me to flourish, succeed and tackle every challenge life brings about.

More so, I would like to thank my dear friend, Jason Kirincich, for all his help writing this thesis and for being my support system throughout the six years of medical school. You have taught me a lot on how to achieve academic excellence and aim as high as you can.

Lastly, I would like to thank the University of Zagreb for giving me the opportunity to fulfill my dream of becoming a medical doctor.

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Biography

Yamit Berl is a soon to be medical doctor who is studying in the sixth and final year in the international medical program in the faculty of medicine, University of Zagreb, Croatia.

She was born and raised on kibbutz Ein Hanatziv, Israel. During high school she volunteered for four years in MDA (Israel's emergency pre-hospital medical service). After completing her 2-year obligatory military service in the Israeli defense force (IDF) as a combat medic and an instructor for the medical corps, she started medical school. In medical school she was chosen as a student representative on the 'eMed student council' for four consecutive years.

After living for six years in Croatia and passing all her exams in excellence, she is ready to begin a new chapter in her medical future.