CLINICAL USEFULNESS OF ^{99M}TC-HYNIC-TOC AND ^{131}I-MIBG SCINTIGRAPHY IN THE EVALUATION OF ADRENAL TUMORS

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KLINIČKI ZNAČAJ SCINTIGRAFIJE SA ^{99M}TC-HYNIC-TOC I ^{131}I-MIBG U EVALUACIJI TUMORA NADBUBREŽNIH ŽLEZDA

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ABSTRACT

Disorders and morphological abnormalities affecting the adrenal gland, could lead to profound clinical consequences, owing to its biochemical structure-activity and morphological characteristics.

The recent focus on theranostic approach has led to a need for tumors characterization and early diagnosis at the molecular level. Many radiotracers have been developed with specific imaging characteristics for the adrenal tumors, by exploiting different physiological mechanisms of uptake and metabolism.

The aim of present study is to provide a prospective confirmation of ^{131}I-MIBG and ^{99m}Tc-HYNIC-TOC scintigraphy, for the evaluation of patients with known or suspected tumors of the adrenal region.

The research is designed as a cross-sectional observational study of the clinical correlates and diagnostic accuracy of radionuclide-based imaging methods in relation to in vitro analysis, clinical manifestations and morphological characteristics of these tumors. Furthermore, the present study also evaluates the usefulness and the clinical impact of each radiopharmaceutical for the detection and management of tumors, and functional imaging modality as well.

Visual scintigraphic appearance of an increased focal tracer uptake in the suspected tumor site revealed that ^{99m}Tc-HYNIC-TOC is highly sensitive and reliable tumor-seeking radiotracer for adrenal tumors, but does not distinguish between adenoma and pheochromocytoma, and the existence of hormone secreting adrenocortical tumor cells. However, ^{131}I-MIBG scintigraphy is highly sensitive and specific method only in differentiating catecholamine-secreting adrenal tumors.

Clinical significance of this research is in the accurate localization of adrenal tumors, and is of paramount importance for an algorithmic diagnostic approach and management, and provide the rationale to different therapeutic possibilities.

Key words: *^{131}I-MIBG, ^{99m}Tc-HYNIC-TOC, adrenal tumors*

SAŽETAK

Ekspanzivni procesi nadbubrežnih žlezda manifestuju se kao poremećaji funkcije i morfologije, i odlikuju izraženom raznolikošću kliničke slike.

Prateći tokove savremene medicine, dijagnostička procedura navedenih poremećaja se sve više fokusira na morfo-funkcionalnu evaluaciju na ćelijskom nivou, i različiti tumorotropni radiofarmaceutici su razvijeni sa ciljem da se potvrdi postojanje i odredi funkcijski status tumora.

Osnovni cilj istraživanja je da se ispitaju parametri dijagnostičke pouzdanosti scintigrafije sa ^{131}I-MIBG i ^{99m}Tc-HYNIC-TOC u evaluaciji ispitanika sa ekspazivnim procesima nadbubrežnih žlezda.

Istraživanje je dizajnirano kao klinička, opservaciona, studija preseka, u cilju ispitivanja parametara dijagnostičke pouzdanosti scintigrafskih metoda, njihove dijagnostičke tačnosti u odnosu na kliničke, laboratorijske i morfološke dijagnostičke parametre. Ispitivane su scintigrafske karakteristike svakog radiofarmaceutika ponaosob, u odnosu na postojanje tumora i njihovu sekretornu aktivnost, kao i utvrđivanje njihove kombinovane prediktivne vrednosti.

Studija je pokazala da se kvalitativnom analizom scintigrama sa ^{99m}Tc-HYNIC-TOC mogu uspešno prepoznati bolesnici sa i bez prisustva nadbubrežnih žlezda, mada ovaj radiofarmacetik ne pokazuje moć distinkcije u smislu adrenalne i medularne propagacije, kao ni za procenu sekretorne sposobnosti adrenokortikalnih tumora. Međutim scintigrafija sa ^{131}I-MIBG ima dijagnostičku korist, i to u diferencijaciji tumora hromafinog tkiva.

Sa kliničkog aspekta, značaj ovog istraživanja je u preciznoj proceni lokalizacije i proširenosti ekspazivnih procesa nadbubrežnih žlezda, što može imati praktični značaj u kreiranju dijagnostičkog algoritma ovih oboljenja, kao i u odabiru adekvatne terapijske opcije.

Ključne reči: *^{131}I-MIBG, ^{99m}Tc-HYNIC-TOC, nadbubrežne žlezde, tumori*

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INTRODUCTION

Primary adrenal tumours encountered in clinical practice comprise a broad spectrum of clinical presentations due to their biochemical structure-activity and morphological characteristics. All neoplasms derived from the adrenal medulla and cortex can give rise to benign or malignant tumours that can be hyperfunctioning or non-functioning (1-3).

While the overall prevalence of adrenal masses are estimated to occur in approximately 9% of the general population (1), the incidence of adrenal nodules at autopsy is between 8.7% and 32% of patients without suspicion of adrenal disease (2, 4-6). Ageing is associated with an increased frequency, the prevalence being <1% among individuals less than 30 years of age to approximately 6% in those over 60 years of age (1, 7, 8). These masses are more frequently unilateral, but in about approximately 15% of cases, they present as bilateral (5, 7-9).

Adrenal adenomas are the most commonly encountered adrenal masses at up to 80%, with myelolipoma accounting for 6% and pheochromocytoma for 3%. (2, 4, 5, 7, 8, 10). The vast majority of these lesions are benign, non-hyperfunctioning adrenocortical adenomas and require no treatment (60-80%), 5–47% secrete cortisol, and 1.1–10% secrete mineralocorticoids, while androgen or oestrogen secreting masses and primary malignancies of the adrenal gland are extremely rare (1, 5, 7, 10, 11). There are no current screening recommendations for adrenal tumours in the general population, except for patients with known or suspected familiar syndromes (1).

Determining the nature of the adrenal mass is often a clinical challenge. Early diagnosis and an appropriate assessment of an adrenal mass is an essential prerequisite prior to its definitive treatment (2, 7, 12)

The initial diagnostic approach includes a clinical and biochemical assessment of cortical and medullary adrenal function and allows for the identification of hypersecreting adrenal lesions. However, a tumour mass may not cause adrenal hyperfunction since it may be non-hypersecreting or secrete non-active products (2, 6, 7, 12, 13).

Improvements in imaging modalities and their interpretation have increased dramatically over the past few years and can now offer a considerable amount of material to help inform clinical decision making (6, 13, 14). Computed tomography (CT) scans and magnetic resonance imaging (MRI) can provide anatomic details of adrenal tumours and often allow malignancy to be ruled out, although a significant portion of patients have indeterminate tumours (7, 8, 13-16). Furthermore, in hormonally non-functioning tumours, differentiating adrenocortical lesions from other lesions is a major diagnostic challenge (5, 10, 17, 18).

Nuclear imaging techniques performed with specifically radiolabelled agents that display unique biological behaviour and target elements of adrenal function may provide specific information for tumour characterization and an estimate of the functional status of the adrenals (19-22). It is non-invasive and complements the imaging data obtained by CT or MRI to further characterize the lesion. (13, 20, 23).

Although $^{131I-}$ and ^{123}I-metaiodobenzylguanidine (MIBG), a norepinephrine analogue whose uptake is proportional to the number of neurosecretory granules within the tumour, is the most common functional imaging technique used in the assessment of pheochromocytomas (21, 22, 24, 25), the scintigraphic evaluation of patients with adrenocortical tumours is currently limited (13, 19, 20, 23).

In recent years, radiolabelled somatostatin analogues that were proposed in the diagnostic evaluation of malignant neuroendocrine tumours reflecting the presence of somatostatin receptors have now been proposed in the diagnostic evaluation of patients with adrenal abnormalities (19, 20, 26-29)

In this research, we describe the role of nuclear medicine imaging using radiolabelled peptide ^{99m}Tc-hydrazinonicotinylacid-d-phenylalanyl^{1}-tyrosine^{3}-octreotide (^{99m}Tc-HYNIC-TOC) and ^{131}I- MIBG in the diagnostic evaluation of patients with adrenal tumours in order to perform lesion characterization and determine the functional status of these tumours.

MATERIAL AND METHODS

Study population

This cross-sectional study was conducted during the year 2016-2017, at the Centre for Nuclear Medicine and the Centre for Endocrinology, Diabetes and Metabolism Diseases, Clinical Centre Kragujevac. The research was conducted in accordance with the Declaration of Helsinki (2005) of the World Medical Association and was approved by the Ethics Committee of the Clinical Centre Kragujevac. After being informed of the study's purpose, risks and benefits, all patients provided written informed consent to participate in the study.

We analysed 27 male and female consecutive patients older than 18 years, who had a documented clinical diagnosis of an adrenal tumour. The control group was comprised 19 patients with clinically diagnosed pituitary adenoma without clinical characteristics of adrenal involvement.

All patients underwent a standardized diagnostic evaluation of hypothalamic–pituitary–adrenal tumours based on biochemical and clinical parameters and imaging criteria (2, 6, 7, 12, 13, 30).

The exclusion criteria were defined in the protocol study. Therefore, some patients were excluded after randomization according to these protocols. The important exclusion criteria were: pregnancy, breast feeding, diseases and administration of drugs influencing hormonal secretion, disorders with a similar clinical presentation, amyloidosis or infiltrative disease potentially affecting the adrenal glands, history of malignant disease and other severe life-threatening diseases (pre-existing coronary and other atherosclerotic vascular disease), and no consent given.

Demographic characteristics collected for patients were: sex, age, socio-demographic characteristics, and data from each patient's medical record and clinical course.

Determination of biochemical parameters

In relation to endocrine functionality, all patients underwent hormone tests related to pheocromocytoma, subclinical Cushing's syndrome, Conn's syndrome or androgen-secreting adrenal tumours. Hormonal studies were performed in all cases, which included plasma cortisol measurement with an overnight dexamethasone suppression test (DST) (screening, low-dose and high-dose), plasma prolactin level, which was determined immunoradiometrically (IRMA Cis-Biointernational, France) measured on a Wallac Wizard 1470 Automatic gamma counter (PerkinElmer Life Sciences, Wallac Oy, 2005, Finland). Plasma adrenocorticotropic hormone (ACTH), serum progesterone, testosterone and β-estradiol, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), plasma free metanephrine and catecholamines, serum aldosterone and plasma renin activity (PRA), which were measured using commercially available enzymatic reagents (Makler d.o.o, Belgrade, Serbia) adapted to an autoanalyser (Olympus AU 400).

Diagnostic imaging

Radiological imaging

In the imaging evaluation, the conventional morphological characteristics was assessed with a 64-row multidetector CT (MDCT) scanner (Aquilion™, Toshiba, Japan). All scans were performed in the axial plane with subsequent multiplanar reconstruction. The standard examination protocol was comprised of a pre-contrast CT to provide density measurements of the lesions. Two post-contrast scans, wash in (WI) at 60 sec and wash out (WO) at 15 min after iodinated contrast agent injection began, can quantify the percentage of absolute or relative contrast enhancement washout and show the vessels in the region of the adrenal glands. We also evaluated Hounsfield Units (HU) before and after contrast media administration in all lesions using a CT examination.

All MRI imaging studies were performed on 1.5-T closed magnet (Magnetom Symphony™, Siemens, Germany). Imaging of adrenal glands included T1- and T2-weighted images, plus chemical shift imaging (CSI) (in-phase and out-of-phase imaging) and/or dynamic-gadolinium sequences. The CSI signal loss on MRI can be quantitatively calculated by measuring the signal intensity index (ASII) using the formula: (SIIP-SIOP)/SIIP x 100% (IP=in phase; OP=opposed phase; S =signal intensity).

Nuclear Medicine Imaging

All patients underwent ^{131}I-metaiodobenzylguanidine (MIBG) whole-body scintigraphy, on dual-head Gamma camera (Syngo-E.cam™, Siemens, Germany), equipped with high energy collimators. After the administration of a thyroid blockade with Lugol solution (1 day before and 3-7 days after) all patients received 370 MBq of ^{131}I-MIBG. 24-48 h after administration, the whole-body planar (anterior and posterior) images were acquired using a dual-head Gamma camera with a window setting of 364 keV. Qualitative uptake intensity was rated according to the following method: 0 if no uptake was present, and 1, 2, and 3 represent tumour uptake less than, equal to, and more than activity in the liver, respectively (30).

Somatostatin receptor scintigraphy (SRS) was also performed in both subject groups, using the commercially available somatostatin analogue ^{99m}Tc-HYNIC-TOC. Whole body scintigraphy was performed 2 h after i.v. administration of 740 MBq in the anterior and posterior projections (256x1024 matrix, 12 cm/min), with a two headed large field of view gamma camera equipped with low energy high resolution collimators at a window setting of 140 keV. The investigation was followed by single-photon emission computed tomography (SPECT) scan of a particular region with the following parameters: 360° noncircular orbit (body contour mode) step and shoot mode, at 30 s per view, 1.23 zoom. The acquired data were collected in a 128x128 image matrix and reconstructed using an iterative ordered subset expectation algorithm. The scoring of the visual uptake (qualitative evaluation) was based on a five-point scale: 0, no uptake; 1, very low/equivocal uptake; 2, clear but faint uptake (less than or equal to liver uptake); 3, moderate uptake (higher than liver uptake); 4, very intense uptake (31).

^{131}I-MIBG and ^{99m}Tc-HYNIC-TOC scintigraphy were performed within at least a 4-week interval.

The images were interpreted qualitatively and independently by 2 experienced nuclear medicine physicians, who were unaware of the other imaging findings and/or other clinical information.

Standard of Reference

For hormone hypersecreting adrenal tumours with typical symptoms and in patients with adrenal incidentaloma larger than 4 cm, a definitive diagnosis was established by pathologic examination (gross pathology, light microscopy and immunohistochemistry evaluation) after surgical resection. For clinically silent adrenal masses with diameters less than 4 cm, a serial clinical follow-up was planned, with clinical, biochemical and CT evaluations, for at least 2 years to ensure a benign diagnosis.

Statistical analysis was performed using SPSS for Windows 20.0 (*SPSS Inc., USA).* Continuous variables are summed as arithmetic means, medians and standard deviations, and categorical variables as proportions (percentages of categories). The estimates of sensitivity, specificity, positive and negative predictive values, and accuracy were obtained with the use of 2x2 contingency tables. The mean±standard deviation were used for continuous vari-

Table 1. Demographic and clinical features of patients with adrenal tumors.

	all adrenal tumors	non-secreting adenomas	hormonally functioning tumors		
			cortisol	aldosterone	catecholamines
no. of adrenal masses	27	13	6	4	4
gender					
male	7	4	0	2	1
female	20	9	6	2	3
age	53,66±11,58	52,38±9,06	54,90±14,59		
diameter mean[a] (cm)	3.45±1.35	4.2±1.6	2.7±1.1		
site					
right	9	5	1	1	2
left	17	8	4	3	2
bilateral	1	0	1	0	0
exams					
CT	20	9	5	4	2
MRI	8	4	1	1	2
CT & MRI	6	3	1	1	1
Scintigraphy[b]	27	13	6	4	4

a. the largest diameters of adrenal lesions was used for analysis
b. ^{131}I-MIBG and ^{99m}Tc-HYNIC-TOC scintigraphy

ables, whereas the number and percentage were used for nominal variables. The alpha level for significance was set to $p<0.05$.

RESULTS

This study included 46 patients. Of those, 27 were diagnosed with an adrenal tumour (AT), 7 were males and 20 were females. The mean age of the patients were 53.66±11.58 years, and the median age was 54.00 years (range 31-71 years). The control group (CG) were a consecutive series of nineteen patients with pituitary tumours without clinical proof of adrenal involvement (2 women and 21 men; average age 47.78±12.78, median age 48.00 with range 24-69 years).

Distribution of clinical parameters in patients with adrenal tumours are reported in Table 1. Androgen-secreting adrenal tumours was been detected in the study population.

All the secreting forms (SF) of AT (13 cases) underwent surgical resection of the adrenal mass (adrenalectomy); 9 patients (64.3%) by laparoscopy and 4 patients (35.7%) by open surgery. Ultrasound or CT-guided fine needle aspiration percutaneous biopsy was performed in 1 case of non-functioning (NF) AT, while in 2 cases with tumours larger than 4 cm adrenalectomy was performed. For clinically silent adrenal masses with diameters less than 4 cm (n=10), a serial clinical follow-up was planned, with clinical, biochemical and CT evaluations, for at least 2 years to ensure a benign diagnosis. One tumour was rated as being most likely benign but could not be classified as adrenocortical or nonadrenocortical because the hormonal assessment did not reveal hormonal activity, and a histopathological analysis was not available because the patient refused both surgery and biopsy.

The biochemical features of AT patients and CG are reported in Table 2. The prevalence of altered parameters of cortisol secretion and DST tests was similar in CG vs NFAT but elevated in cortisol secreting forms. A similar trend was found for the prevalence of catecholamines and aldosterone secreting AT and their concomitant hormones and metabolites.

The location, size and shape of the lesions were determined with MDCT and MRI and it was found that 23 of the 27 subjects had features of adrenal tumours. Twelve of these were NF of AT, with 4.2±1.6 cm for the largest diameter. Measurement by nonenhanced MDCT revealed a mean value of -13.5±7.6 HU. A semiquantitative study of pre and postcontrast media injection on MDCT at 60 s WI and 15 min WO revealed an adenoma-like appearance with less than 20 HU.

Cushing syndrome was detected in 4 patients, Conn's syndrome in 3 and pheochromocitoma in 3 cases, with a non-enhanced MDCT mean value of -4.5±2.1 HU, and between 20 and 30 HU on postcontrast media injection. Conversely, measurements less than 10 HU were observed in one patient with pheochromocitoma.

Based on findings from conventional MRI imaging, qualitative and quantitative analyses of chemical-shift techniques, the diagnosis of adenoma was made in 6 of 8 patients. Two adrenal masses were diagnosed as pheochromocytomas and 4 as NF adrenal lesions.

The chemical shift in MRI with a cut-off of 16.5% did not demonstrated substantial differences between these two groups of AT. The small number of cases diagnosed with MRI in our study did not allow for the determination of a reliable threshold value in the signal intensity ratio between secreting and non-secreting forms of adrenal tumours.

Despite the sharp anatomic detail of MDCT or MRI, the evaluation with adrenal scintigraphy in conjunction

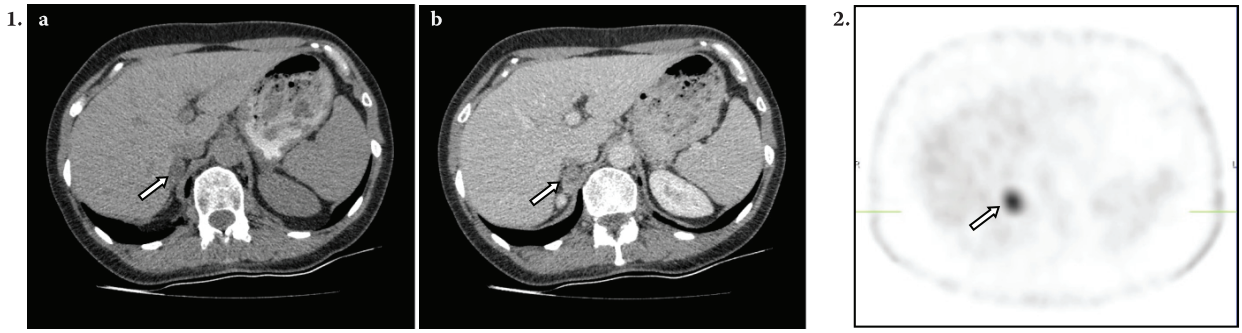
Table 2. Patients results of biochemical parameters

	control group (n=19)	non-secreting adenomas (n=13)	hormonally functioning tumors (n=14)			
			all tumors	catecholamines	aldosterone	cortisol
	median (range)	median (range)	median (range)	median (range)	median (range)	median (range)
cortisol 8h. (154-638nmol/L)	449,50 (305-881)	418,50 (171-790)	534,00 (305-1281)	416,50 (305-591)	468,50 (331-606)	792,00 (534-1281)
cortisol 16-20h. (80-388nmol/L)	275,00 (106-722)	132,50 (92-189)	256,00 (198-556)	152,50 (142-163)	176,60 (50-303)	227,00 (198-556)
cortisol 24h. (50-200nmol/L)	165,52 (133-204)	46,95 (21-85)	194,00 (49-214)	58,40 (21-204)	122,00 (49-195)	161,00 (108-214)
DST "screening" (<150nmol/L)	39,00 (20-620)	39,00 (11-703)	147,00 (28-1455)	95,60 (30-101)	46,40 (28-65)	375,00 (193-1455)
DST "low-dose" (<150nmol/L)	391,50 (38-451)	40,50 (8-495)	175,00 (37-1381)	56,55 (37-75)	-	396,00 (175-1381)
DST "high-dose" (<50% базалног)	172,65 (21-449)	28,00 (9-96)	190,00 (25-1423)	50,10 (24-75)	-	376,00 (190-1423)
ACTH (7,2-63,3pg/mL)	21,32 (5-175)	21,75 (5-39)	5,00 (1,7-63,8)	-	-	5,0 (1,7-63,8)
aldosterone-rest (1,76-23,20ng/dL)	6,02 (5,2-8,5)	5,61 (4,3-8,5)	10,55 (3,8-79,3)	14,1 (4,4-32,1)	41,55 (3,8-79,3)	-
PRA-rest (2,8-39,9μIU/mL)	12,6 (2,1-40,4)	10,00 (2,1-40,4)	1,30 (0,9-6,3)	-	1,30 (0,9-6,3)	-
aldosterone-stress (2,52-39,2ng/dL)	33,15 (9,3-57,0)	15,95 (2,3-29,6)	33,15 (9,3-57,0)	-	33,15 (9,3-57,0)	-
PRA- stress (4,4-46,1μIU/mL)	12,41 (5,5-19,3)	12,41 (5,5-19,3)	1,60 (0,8-2,4)	-	1,60 (0,8-2,4)	-
β-estradiol 8h. (28-156pmol/L)	39,00 (4-249)	39,00 (7-90)	13,00 (4-249)	-	-	13,00 (4-249)
progesterone 8h. (0,7-4,3nmol/L)	0,50 (0,2-2,4)	0,50 (0,2-1,5)	1,45 (0,2-4,0)	-	-	1,45 (0,2-4,0)
testosterone 8h. (1,73-7,74ng/mL)	0,62 (0,1-3,9)	0,90 (0,3-3,9)	0,39 (0,2-45,0)	-	-	0,39 (0,2-45,0)
FSH 8h. (1,27-19,2mIU/L)	8,29 (1-157)	9,74 (3,3-157,0)	7,00 (2,1-54,2	-	-	7,00 (2,1-54,2)
LH 8h. (1,1-8,6mIU/L)	7,05 (1-60)	7,05 (2,3-89,8)	12,00 (1,2-17,8)	-	-	12,00 (1,2-17,8)
epinephrine (0-27μg/dU)	17,14 (3,98-39,0)	10,29 (3,9-39,0)	5,30 (3,8-88,0)	46,65 (5,3-88)	-	8,64 (3,8-13,5)
norepinephrine (0-97μg/dU)	122,16 (8-305)	88,30 (72-305)	72,80 (19-1169)	642,25 (115-1169)	-	45,86 (19-73)
f-metanefrine (<90pg/ml)	31,60 (17,0-80,5)	25,37 (0,5-80,5)	89,85 (18,3-473,8)	164,80 (121,1-473,8)	22,20 (17,2-27,2)	38,30 (18,0-58,6)

Table 3. Accuracy of ^{99m}Tc-HYNIC-TOC scintigraphy in characterization of adrenal tumors

	sensitivity (%) (95% CI[a])	specificity (%) (95% CI[a])	accuracy (%)	predictive value	
				positive (%) (95% CI[a])	negative (%) (95% CI[a])
all adrenal tumors (n=46)	77.78 (57.74-91.38)	89.47 (66.86-98.70)	82.60	91.30 (71.96-98.93)	73.91 (51.59-89.77)
hormonally functioning tumors (n=27)	57.14 (35.14-87.24)	38.46 (13.86-68.42)	51.85	52.94 (27.81-77.02)	50.00 (17.71-81.29)

a. confidence interval



1. A transaxial MDCT image: a) without contrast enhancement shows a homogenous circumscribed well delineated tumor in the right adrenal gland (arrow) with HU of 7. b) At 60 seconds post contrast, the HU measures 43, and at 15 minutes demonstrates a HU of 18.
2. ^{99m}Tc-HYNIC-TOC SPECT transaxial image at the same patient: solitary extremely somatostatin-avid tracer uptake in the right adrenal gland (arrow) confirming the diagnosis of an adenoma.

with hormonal analysis was used not only in defining the function of adrenal lesions but also in the diagnosis and staging of tumours of adrenal origin.

The ^{131}I-MIBG uptake was positive in all 4 cases of pheochromocytomas (grade 3 uptake was found in 3 and grade 4 in one case of these tumours). Only in one case of adrenocortical tumour was grade 1 uptake noticed.

SRS with ^{99m}Tc-HYNIC-TOC was performed in 27 patients with adrenal tumours and 19 in the control group. The qualitative uptake of the tracer was compared with clinical and biochemical assessments of adrenal function, radiological imaging modalities and histopathologic examination after surgery and/or biopsy. A concordant scintigraphic pattern, defined as an increased radiotracer uptake at the side of the detected mass, has been proposed as a typical pattern of an adrenal tumour (Figure 1). In contrast, a discordant pattern with absent or decreased uptake by the adrenal mass may indicate physiologic accumulation. Table 3 summarizes the diagnostic potential of ^{99m}Tc-HYNIC-TOC scintigraphy for localization of the primary adrenal tumour and for assessment of adrenal function. Interestingly, ^{99m}Tc-HYNIC-TOC scintigraphy identified all cases of the 4 adrenal pheochromocytomas, which is similar to ^{131}I-MIBG imaging.

With histology as the gold standard, the correct diagnosis was missed with radiological imaging in 5 (18.5%) of 27 patients. All these cases were scintigraphy–positive (Table 4).

Patients with <4 cm diameter adrenal lesions, with endocrine negative tests, were sent to six months laboratory follow-up, with CT after 12 months then every year for three years, and an annual endocrine re-evaluation.

DISCUSSION

The detection of an adrenal tumour requires a multidisciplinary approach. Initial clinical and biochemical work-up is usually performed by an endocrinologist because primary tumours in the adrenals can be hyperfunctioning and produce excess hormones from the cortex or the medulla and are accompanied by clinical symptoms (2, 7, 12).

The gender distribution among patients with adrenal tumours appears to vary in different series, but females are still commonly affected, which was the case in our study (80.4%). They occur at all ages but are most common in the fourth to sixth decade of life (5, 6, 8, 10, 11,

Table 4. Discordant result of MDCT and MRI imaging and pathology reports of adrenal masses

Patient No.	Age	Sex	Size (cm)[a]	Hystopathology diagnosis	MRI	MDCT	^{99m}Tc-HYNIC-TOC	^{131}I-MIBG
1	54	female	3.6	adrenocortical adenoma	inconclusive/ metastatic	-	positive (grade 3)	negative
2	65	female	3.8	adrenocortical adenoma	carcinoma		positive (grade 4)	negative
3	59	male	4.0	pheochromocitoma	-	adenoma	Positive (grade 3)	positive (grade 3)
4	32	female	2.8	adrenocortical adenoma		negative	positive (grade 2)	negative
5	63	female	2.5	adrenocortical adenoma		hypodense structure	positive (grade 2)	negative

a. the largest diameters of adrenal lesions

13). The recorded mean age in our study of 53.66±11.58 (range 31-72 years) is in accordance with results reported in our region (32, 33). Several large series reports have found the majority of adrenal adenomas are less than 4 cm in largest diameter (5, 8, 10, 11, 13). Our data correspond to these results, with a median diameter of 3.45±1.35 cm (range, 1.0–15.0 cm) in clinically diagnosed tumours.

The results of the present study demonstrate that adrenal cortical tumours were more common than medullary tumours, accounting for 85.2% of cases. Our study partially matches with the observation of others regarding the tumour type (4, 5, 7, 8, 34), with non-functioning accounting for approximately 48.1% of all adrenal tumours followed by cortisol-secreting adenoma noted in approximately 22.2%, and aldosterone-secreting adenoma in 14.8%. Other types of adrenal tumours, including adrenocortical carcinoma, were not detected in our study population. Although 60-80% of adrenal tumours are asymptomatic with a size less than 4 cm, the main recommendation is to consider all adrenal incidentaloma as a hypersecreting tumour, even without clinical manifestation until otherwise proven by hormonal tests (2, 7, 12). Clinical and biochemical features of tumours seen in our study resulted in the over-production of hormones and metabolites, with over half of all patients developing marked symptoms. Subclinical cortisol-producing adenomas were well recognized and reported to be higher in our study.

The management of adrenal tumours poses a therapeutic dilemma. All patients should undergo hormonal screening to assess functionality and specific radiological imaging and/or scintigraphy in order to recognize lesion-type, assess lesion function and to differentiate between benign and malignant tumours (2, 7, 12, 35).

MDCT is often the first modality utilized in detecting adrenal masses. The sensitivity to differentiating malignant from benign adrenal tumours ranges from 79 to 89% in studies and with specificities of 87-96% (5, 13, 17, 18). Adrenal adenomas may be suggested by CT on the basis of a low attenuation coefficient without enhancement to contrast media images and/or early as well as rapid washout on enhanced scans. A lesion with smooth margins, a size less than 4 cm and density <10 HU without enhancement to contrast media indicates lipid-rich adenomas, although 25–30% of adenomas are lipid poor and have CT attenuation values >10 HU. A density of -10 HU is characteristic of a myelolipoma; if the attenuation is 0-15 HU without enhancement a simple cyst is suspected, while malignant tumours have high pressure impeding the contrast-enhancement and delaying the contrast medium wash-out (5-8, 14. 15, 17, 18).

In our study, most (87%) adenomas were characterized on unenhanced CT using a threshold of ≤10 H. Interestingly, in our series 10% of adenomas were diagnosed in routine contrast enhanced studies using an identical threshold.

Pheochromocytomas can have a varied appearance on non-contrast CT ranging from low-density to soft-tissue attenuation. Although the vast majority have an attenuation value greater than 10 HU, rare low-density pheochromocytoma can have attenuation values similar to adenomas (21, 22, 34, 36, 37), which was the case in our study. The mean arterial and venous phase enhancement of pheochromocytomas in the 2 cases presented in our results was significantly higher than that of adenomas.

MRI is indicated for characterization of adrenal masses that show atypical findings on MDCT. Adrenal adenomas usually present on MRI as isointense or with low signal intensity on T1- and T2-weighted images and rapid contrast and washout after gadolinium administration, although they may contain insufficient lipids, resulting in a loss of signal on the out-of-phase scan (6, 8, 13,16). MRI is superior than MDCT in the characterization of carcinoma infiltration. The presence of calcifications, necrosis and haemorrhage is suspicious but not pathognomonic for malignancy, which show low signal intensity on T1-weighted images and high signal intensity on T2-weighted images with strong enhancement and slow washout after contrast media administration (11, 14, 15). MRI effectiveness was previously reported to correspond to a diagnostic accuracy of 93% to differentiate between benign and malignant adrenal masses. However, on T2-weighted images 30% of lesions present overlapping between benign and malign tumour appearance, such as adrenal carcinoma and metastatic lesions (10, 11, 17, 36, 38). All this may reduce the accuracy of this imaging modality.

The reason for misdiagnosing two adenomas in our study can be explained partially by the fact that for 1 patient a chemical-shift MRI was not available, and the dynamic studies showed a marked enhancement after injection of gadolinium. On the second MRI imaging, 1 adrenal mass that was classified as metastases proved to be a benign adenoma at histology.

Pheochromocytomas show specific MRI features such as a clearly increased signal intensity on T2-weighted images and significant enhancement after gadolinium administration. On T1-weighted sequences, pheochromocytomas are typically isointense or hypointense to muscle (21, 22, 34), which was the case in our study. However, the appearance can be quite variable if there is necrosis or haemorrhage present, which would be hyperintense on both T1- and T2-weighted sequences. Pheochromocytoma can even have low signal intensity on T2-weighted sequences in approximately 35% of cases (15, 36-38).

The main purpose of this study was to evaluate the use of scintigraphic modality in the assessment of AT in order to allow the clinician to make a precise diagnosis and customize the treatment accordingly. Due to the potential overlap in CT and MRI appearances of different tumour types, functional imaging can be helpful for characterizing the nature of AT and to differentiate between cortical and medullar adrenal masses.

MIBG imaging has been well established as a localizing tool and a functional marker of catecholamine secreting tissue, with a high sensitivity range (83%-100%) and a high specificity (95–100%) (24, 25, 30). MIBG demonstrated a high diagnostic accuracy in four patients, who had pheochromocytomas confirmed by histopathology and were positive on the MIBG scan. On the basis of our findings, nuclear imaging modalities using MIBG are able to better characterize pheochromocytomas compared with MRI (1 was misdiagnosed). All other types of AT were MIBG negative, except one case of AT with a faint uptake (grade 1) that was characterized as physiologic adrenal uptake. Comparative studies between MIBG and MRI demonstrated that MIBG uptake in patients with pheochromocytoma is able to differentiate between benign and malignant tumour lesions, while MRI is not useful for this purpose (15).

Somatostatin receptor scintigraphy is currently widely utilized in clinical practice and has been extensively investigated for imaging of sympathomedullary and other neuroendocrine tumours (28-31). This uptake is related to the widespread distribution of cells expressing somatostatin receptors (SSTR), especially type 2 SSTR, in the majority of neuroendocrine tumours, including the adrenal gland (26, 27). The results of various studies revealed that somatostatine radiolabelled analogues (^{99m}Tc-HYNIC-TOC) are a second choice technique for sympathomedullary imaging after MIBG scintigraphy, especially when the MIBG is completely or partly false negative. Conversely, due to its high sensitivity ^{99m}Tc-HYNIC-TOC scintigraphy can be considered as the first choice scintigraphic imaging technique in paragangliomas. (24, 25, 30, 31, 39).

Encouraged by the high sensitivity of SRS in localizing pheochromocytoma and paragangliomas we also performed ^{99m}Tc-HYNIC-TOC scintigraphy in a group of patients with adrenal adenomas. The results of the *in vitro* studies demonstrate that somatostatin receptors are expressed in adrenal tumours in a varied manner, which is specific in each case (26-28).

Successful detection was achieved in majority of the AT with a sensitivity of 77.78%, and a specificity of 89.47%. In contrast, ^{99m}Tc-HYNIC-TOC scintigraphy has a lower diagnostic potential in differentiating the form of these tumours (sensitivity of 57.14%, and specificity of 38.46).

All four of our patients diagnosed with pheochromocytomas were positive on ^{99m}Tc-HYNIC-TOC scintigraphy (three cases with grade 3, one case with grade 2).

Scintigraphy using specific tracers such as ^{131}I-MIBG and ^{99m}Tc-HYNIC-TOC may provide *in vivo* tissue characterization of adrenal tumours. Based upon the present results, somatostatin-receptor analogues can be front-line radiotracers in the imaging of adrenocortical and adrenomedullary tumours, respectively, while performing SRS for hormone secreting forms of adrenocortical adenomas is not advised. ^{99m}Tc-HYNIC-TOC positive scintigraphy accompanied with MIBG negative scintigraphy is likely to belong to the adrenocortical adenoma.

CONCLUSION

On the basis of our findings, nuclear imaging modalities using specific tracers are able to characterize AT with a high sensitivity and specificity compared with MRI and MDCT. Functional scintigraphy using SPECT modality complements anatomy-based imaging and facilitates diagnostic localization. In particular, radionuclide techniques are able to identify the existence of AT and to differentiate between adenoma and pheochromocytoma. Furthermore, whole-body imaging allows the detection of extra-adrenal phaeochromocytomas, multifocal disease, metastatic disease and residual/recurrent tumour. Our data show considerable clinical promise for the future and provide the rationale of different diagnostic and therapeutic possibilities of somatostatin analogues in adrenal tumours.

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