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Original Research

Comparative Analysis of FSE T2 Weighted, Chemical Shift and Dynamic Contrast-Enhanced MR Imaging in the Characterization of Adrenal Masses Based on Qualitative and Quantitative Parameters

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Abstract

Objectives: The purpose of our study was to investigate the role of different magnetic resonance imaging (MRI) parameters in the characterization of adrenal masses.

Methods: A total of 150 patients who presented with 186 adrenal tumors were retrospectively evaluated in this study. Final patient cohort consisted of 17 pheochromocytomas, 3 adrenocortical carcinomas, 24 metastases, 31 lipid-poor adenomas and 111 lipid-rich adenomas. We carried out a visual assessment on FSE (Fast spin echo)T2 weighted images and also calculated T2 signal intensity ratio of all adrenal masses and also performed a qualitative assessment on chemical shift imaging (CSI) together with quantitative calculation using Adrenal to spleen signal intensity (si) ratio and Adrenal si index formulas. On dynamic contrast-enhanced sequences, visual assessment based on enhancement patterns on late-arterial phase images was performed and also mean signal intensity measurements were carried out. All examinations were interpreted by two abdominal radiologists in consensus who were blinded to the clinical and pathological findings. Statistical analysis was performed.

Results: On FSE T2 weighted imaging, isointense to liver and slightly hyperintense than liver was found higher in benign cases, however, in malignant cases moderately and strikingly hyperintense than liver was higher than in benign cases ($p=0.001$, $p<0.01$). There was a statistically significant difference between the T2 signal intensity ratio values of adrenal tumor groups ($p=0.001$, $p<0.01$). In lipid-rich and lipid-poor adenoma groups, T2 signal intensity ratio values was significantly lower than in pheochromocytoma and metastasis cases. In malignant group, T2 signal intensity ratio values were found statistically significantly higher than in the benign group ($p=0.001$, $p<0.01$). There was a statistically significant difference between CSI visual assessment of adrenal tumor groups ($p=0.001$, $p<0.01$). Although moderate and significant signal intensity loss was usually detected in lipid-rich adenoma group, never detected in other tumor groups. There was also a statistically significant difference between benign and malignant adrenal tumor groups ($p=0.001$, $p<0.01$). In the malignant group, Adrenal to spleen si ratio values were found significantly higher whereas, Adrenal si index values were significantly lower compared to benign tumors ($p=0.001$, $p<0.01$). Based on malignancy, there was a statistically significant difference between adrenal tumor groups ($p=0.001$, $p<0.01$). Although capillary blush and homogenous type enhancement were more common in benign cases than in malignant ones, peripheral-patchy and strikingly capillary blush type enhancement was more frequent in malignant tumors. Based on malignancy, mean arterial signal intensity values of malignant tumors were statistically higher than benign tumors ($p=0.001$; $p<0.01$).

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Abstract

Conclusion: Dynamic contrast-enhanced MRI protocol including CSI aids in the characterization of indeterminate adrenal masses. Herein, the combined use of qualitative and quantitative parameters enables more tumors to be recognized that otherwise would be indeterminate.

Keywords: Adenoma, adrenal, adrenal metastases, contrast-enhanced MRI, pheochromocytoma

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Adrenal lesion detection has increased in recent years due to widespread use of cross-sectional imaging modalities and has an incidence of 4-5% in patients who undergocomputed tomography (CT) examination.[1] Most of these adrenal masses turned out to be adenomas, even in patients who have a history of primary extra-adrenal malignancy.[2] Although the most commonly seen adrenal nodule is adenoma in the general population,[2,3] other type of pathologic entities including metastasis, pheochromocytoma and adrenocortical carcinoma (ACC) should also be considered in the differential diagnosis of adrenal tumors. Another type of incidentally discovered adrenal mass is myelolipoma which contains macroscopic fat, soft tissue components and calcification and these specific imaging features enable it easily to be distinguished from that of adenoma. CT and magnetic resonance imaging (MRI) evaluation of adrenal glands can provide some key distinguishing imaging features that may help to differentiate adrenal adenomas from nonadenomas and thereby can lead to a substantial decrease in the number of adrenal mass biopsies.[4] Non-invasive differentiation of benign adrenal masses from malignant ones carries crucial importance in terms of decision-making about management and treatment strategies and also to predict the prognosis of patients. Although follow-up imaging is recommended in benign cases, different approach protocols are used for malignant ones.

Unenhanced CT scans can characterize lipid-rich adenomas by detecting their intracytoplasmic lipid content which causes a decrease in attenuation values. A commonly applied attenuation threshold value of less than 10 HU (Hounsfield unit) has a sensitivity of 71% and specificity of 98% for lipid-rich adenoma diagnosis.[5] However, approximately one-third of adenomas do not have sufficient intracytoplasmic lipid content, so-called lipid-poor adenomas, which result in CT attenuation values greater than 10 HU.[5,6] Some studies showed that CT histogram analysis method using a more than 10 % negative pixel threshold value yielded 84-91% sensitivity and 100 % specificity for adenoma characterization.[7,8] Although somehow time-consuming, it can reliably be applied in renal insufficiency patients and iodine contrast-sensitive individuals. The most reliable MRI technique in the characterization of adrenal nodules is chemical shift imaging (CSI). It relies on the fact that adenomas contain a substantial amount of intracytoplasmic lipids whereas other adrenal masses do not. Besides, on T2 weighted MRI sequences, adenomas are usually seen as homogenous and exhibit low to intermediate signal intensity than liver and muscles unless they undergo cystic degeneration which is responsible for their heterogeneous appearance.[9,10] Dynamic contrast-enhanced MRI studies have also been shown to be useful in the discrimination of benign adenomas from malignant tumors.[11] Diffusion-weighted imaging (DWI) is not beneficial in the discrimination of adenoma from nonadenoma cases because substantial overlapping occurs between apparent diffusion coefficient (ADC) measurements.[12,13] For PET-CT examinations, adrenal masses displaying higher Fuorine- 18-fludeoxyglucose (18F - FDG) values compared to liver parenchyma can be considered as malignant lesions. Although PET-CT has a higher accuracy than wash-out CT for diagnosis of metastatic lesions, a combination of both techniques provides better results than using either of them alone.[14] Our purpose in this study was to investigate the utility of different MRI parameters composed of T2 weighted visual assessment and T2 signal intensity ratio, qualitative and quantitative CSI on the basis of formulas and qualitative and quantitative evaluation of late-phase arterial contrast-enhanced images for differential diagnosis of various adrenal tumors.

Methods

Patient Cohort

Our hospital Instutitional Research Ethics Committee approved this retrospective study and informed consents were avaliable for the patients. In our study, Helsinki declaration criteria were applied. Between april 2014 and january 2022 years, we performed a retrospective based search including all type adrenal tumors who underwent CSI and dynamic contrast-enhanced MRI using picture archiving and communication system (PACS Medical workstation, Siemens Medical Systems, Erlangen, Germany). Our inclusion criteria were as follows: Adequate image quality

without motion artifacts, adrenal mass size at least 1 cm., avaliability of fast spin echo (FSE) T2 weighted images, CSI sequence with dual-echo gradient-recalled echo in-phase and opposed phase images and late-arterial phase dynamic contrast-enhanced MR images. After applied these criteria, we identified a total of 150 patients presenting with 186 adrenal tumors. Among them 17 patients had pheochromocytomas, 24 had metastases, 3 had adrenocortical carcinomas (ACCs), 31 had lipid-poor adenomas and 111 patients had lipid-rich adenomas. Bilateral lesions were found in 2 patients with pheochromocytomas, 8 patients with metastases and 26 patients with adenomas. 89 tumors (47.8 %) were located on the right and 97 tumors (52.2 %) were on the left. Patient cohort consisted of 62 (41.3 %) males and 88 (58.7 %) females. Mean age of patients was found as 55,95±11,76. Mean diameter of tumors were 32.82±18.65 mm., 32.75±26.52 mm., 87.67±34.56 mm., 21.77±16.87 mm., and 22.44±9.46 for pheochromocytomas, metastases, ACCs, lipid-poor and lipid-rich adenomas, respectively. In metastasis group, primary malignancies consisted of 7 lung carcinoma, 6 renal cell carcinoma, 3 hepatocellular carcinoma, 2 colorectal carcinoma, 2 gastric carcinoma, 2 malignant melanoma, 1 breast carcinoma and 1 ovarian carcinoma. CT was avaliable in 9 pheochromocytoma, 12 metastasis and 69 adenoma cases and mean attenuation values were obtained in these patients. We used different type reference standards for benign and malignant adrenal tumors. For benign appearing highly probable adenoma cases, we applied American College of Radiology (ACR) White Paper guidelines criteria which based on during a follow up of 12 months or longer, if a mass has not shown a change in its size and stability can be regarded as benign.[15] We also used mean CT attenuation threshold value of less than 10 HU as a criterion for lipid-rich adenoma diagnosis, if it accompanied to MRI examination and was avaliable in our PACS. Regarding malignant adrenal tumors, we applied multiple criteria including large tumor size, irregular margins, coexistant primary extra-adrenal malignant tumor, multiple metastases elsewhere, histopathological confirmation after fine-needle aspiration biopsy and surgical excision, increase in tumor size during follow-up imaging, respond to chemotherapy with reduced tumor volume and positron emission tomography (PET) CT findings. Clinical findings and biochemical analysis were also beneficial in the diagnosis of pheochromocytoma cases. These patients showed increased 24-hour urine fractionated metanephrine and catecholamine levels.

MR Imaging Technique and Data Analysis

All MR images were obtained via a torso phased-array coil on a 1.5 tesla clinical scanner (Avanto- SQ Engine, Siemens, Erlangen, Germany). Our parameters for T2 weighted FSE sequence were TR: 7500 msec., TE: 85 msec., Echo train length (ETL): 20, Nex: 1, bandwidth: 260 Hz, on the axial or coronal plane. For CSI, T1 weighted, axial plane, dual-echo in-phase and opposed-phase gradient echo (GE) images were obtained at the same breath-hold. This was achieved with 2D sequences applying TEs at approximately 2.2 and 4.4 msec for in-phase and out-of-phase images, respectively. Dynamic contrast-enhanced MRI was performed using an axial plane T1 weighted 3D GE sequence with fat-suppression technique before and after administration of 0.1 mmol/kg intravenous gadolinium DTPA injected at a rate of 2 mL/sn followed by 20 mL. boluse saline flush. Slice thickness: 6 mm. and Gap: 1.2 mm. All examinations were evaluated by experienced (A.M.H.) and resident (B.V.B.) abdominal radiologists who were blinded to the patients' final diagnoses. Qualitative and quantitative evaluations were performed and recorded in consensus. Qualitative evaluation on FSE T2 weighted images was performed using liver and cerebrospinal fluid (CSF) as reference organs. Adrenal masses were categorized as hypointense, isointense, slightly hyperintense, moderately hyperintense and markedly hyperintense compared to these reference organs. For quantitative evaluation on FSE T2 weighted and CSI in phase and out of phase GE images, a circular region-of-interest (ROI) was placed on the largest portion of lesion covering approximately two-third of the lesion while avoiding compass the edges of the lesion in order to eliminate partial volume effects and chemical shift artifacts, respectively. On FSE T2 weighted images, a standard 10 mm2 ROI was also placed on the ipsilateral erector muscle and T2 weighted signal intensity ratio was calculated by using that formula:[16]

$$\text{Lesion to muscle signal intensity ratio} = \frac{\text{Lesion SI}}{\text{Muscle SI}}$$

On CSI, a qualitative assessment comparing relative signal intensity changes between in-phase and outof-phase GE images was performed. On the basis of visual evaluation, negligible or absence of signal intensity drop was regarded as no signal intensity change whereas a range of moderate to high signal intensity drop was considered as a significant signal intensity loss. For CSI signal intensity measurements, ROIs were placed on adrenal lesion and spleen on in-phase and out-of-phase GE images. We used Adrenal to spleen si ratio and Adrenal si index formulas as follows :

$$\text{Adrenal to spleen si ratio} = \frac{\text{Lesion SIOP / Spleen SIOP}}{\text{Lesion SIIP / Spleen SIIP}}$$

$$\text{Adrenal si index} = \frac{\text{Lesion SIIP-Lesion SIOP}}{\text{Lesion SIIP}} \times 100$$

Table 1. The distribution of adrenal tumor groups according to sex, age and tumor size parameters

	Tumor groups										p
	Lipid-rich adenoma (n=111)		Lipid-poor adenoma (n=31)		Metastasis (n=24)		•ACC (n=3)		Pheo (n=17)		
	n	%	n	%	n	%	n	%	n	%	
Sex											
Female	80	72.1	16	51.6	4	16.7	1	33.3	7	41.2	[a]0.001**
Male	31	27.9	15	48.4	20	83.3	2	66.7	10	58.8	
Age											
Average±SD	57.55±10,32		57.10±11,56		58.13±8.67		55.00±19.67		40.53±13.5		[b]0.001**
Median (min-max)	57 (37-80)		60 (35-75)		57.5 (39-74)		58 (34-73)		35 (18-65)		
Size (mm)											
Average±SD	22.44±9.46		21.77±16.87		32.75±26.52		87.67±34.56		32.82±18.65		[b]0.001**
Median (min-max)	22 (10-52)		17 (10-84)		23.5(11-126)		90 (52-121)		25 (11-69)		

•: Not included in the comparison due to insufficient number of observations, [a]: Fischer Freeman Halton Test, [b]: Kruskal Wallis Test, **: p<0.01. ACC: Adrenocortical carcinoma, Pheo: Pheochromocytoma.

Commonly accepted threshold values of less than 0.71 and greater than 16.5 % for Adrenal to spleen si ratio and Adrenal si index formulas, respectively, have been proven to exhibit a high accuracy for adenoma diagnosis at 1.5-tesla magnets.[17]

Qualitative evaluation on dynamic contrast-enhanced MRI was made on late-arterial phase images and adrenal lesions were classified into some basic categories based on contrast enhancement patterns. These were strikingly capillary blush, capillary blush, homogenous, hypovascular and peripheral-patchy. Quantitative evaluation was also performed on these late-arterial phase images by placing a ROI on the lesion in a similar fashion as previously mentioned, in order to measure mean signal intensity values.

Statistical Analysis

NCSS (Number Cruncher Statistical System, 2007, Kaysville, Utah, USA) was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used while evaluating the study data. The conformity of the quantitative data to the normal distribution was tested with the Shapiro-Wilk test and graphic examinations. Mann-Whitney U test was used for comparisons between two groups of quantitative variables with normal distribution. Fisher-Freeman-Halton exact test was used to compare qualitative data. Diagnostic screening tests (sensitivity, specificity, PV+, PV-) and ROC analysis were used to determine the cutoff value for the parameters. Statistical significance was accepted as p<0.05.

Results

There was a significant difference in terms of sex and age distribution between the adrenal tumor groups (p=0.001, p<0.01). In our study group, lipid-rich adenomas were seen as significantly more common in females than males, whereas metastatic lesions were more in males. The mean age of patients with pheochromocytoma cases was lower than those with metastasis, lipid-rich adenoma and lipid-poor adenoma patients (p=0.001, p=0.001, p=0.001, p<0.01). There was also a significant difference in mean diameter of adrenal tumor groups (p=0.001, p<0.01). The mean diameter of ACC tumors was found significantly larger compared to the other tumors. There was no significant difference between mean diameters of other tumors than ACC. ACC tumors (87.67±34.56 mm) as was expected, exhibited huge dimensions (Table 1).

Qualitative T2 signal intensity visual assessment of adrenal tumors was compared to liver and cerebero-spinal fluid (CSF). All types of adrenal tumors showed lower signal intensity than CSF, except for pheochromocytomas whose signal intensity was usually found equal to CSF. When compared to liver; 15 pheochromocytomas were strikingly hyperintense and 2 were moderately hyperintense than liver and in 3 ACCs; all of them were moderately hyperintense than liver. In metastases group; 6 were strikingly hyperintense, 11 were moderately hyperintense, 2 were slightly hyperintense and 5 were isointense to liver. In lipid-poor adenoma group; 4 were slightly hyperintense, 7 were moderately hyperintense and 20 were isointense to liver and in lipid-rich adenoma group ; 25 were slightly hyperintense, 6 were moderately hyperintense and 80 were isointense to liver. There was a statistically significant difference between T2 signal intensity visual assessment of adrenal tumor groups (p=0.001, p<0.01). In pheochromocytoma cases, strikingly hyperintense than liver is found significantly

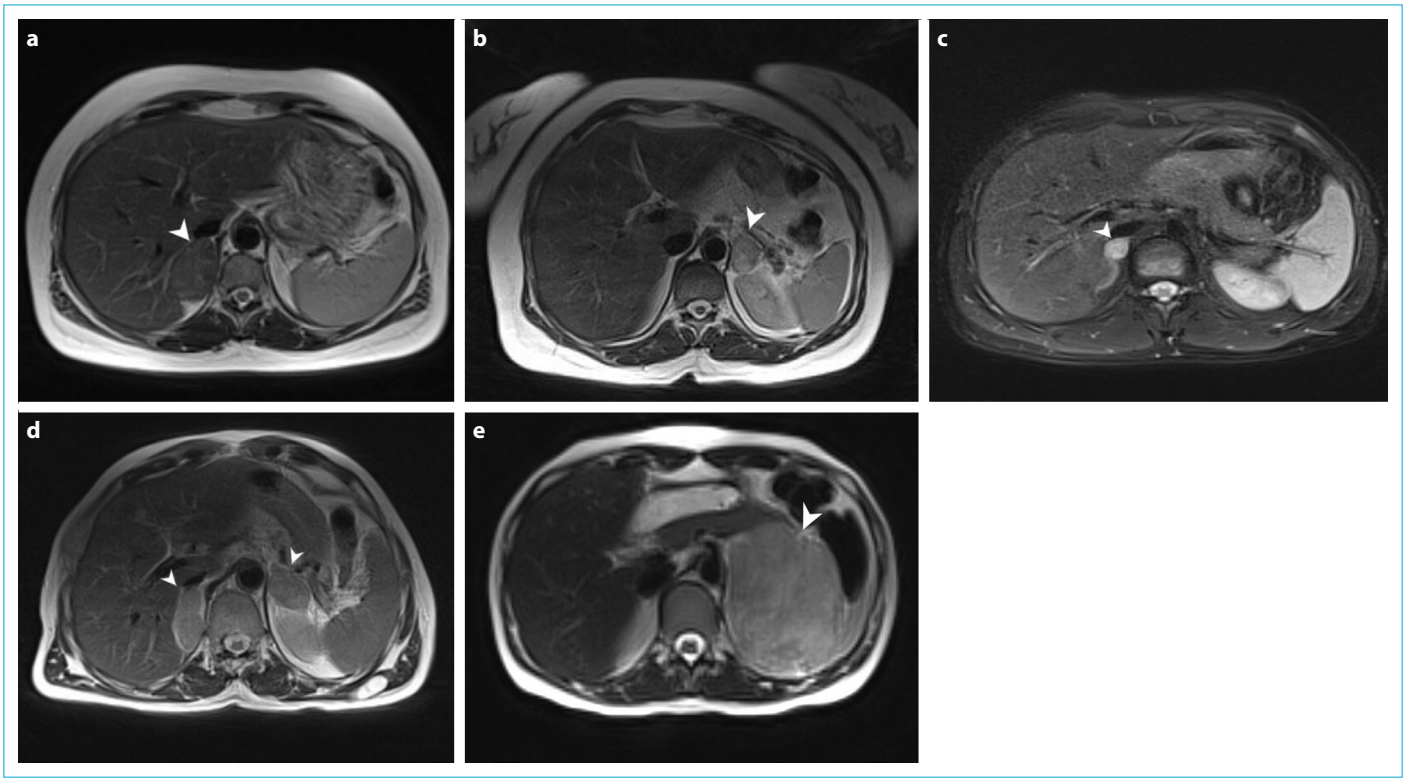

Figure 1. FSE T2 weighted imaging visual assessment of different type adrenal tumors. **(a)** 44 year-old-woman with 4.2 cm. right adrenal lipid-rich adenoma. T2 weighted signal intensity is seen as isointense to liver. **(b)** 53 year-old-woman with 2.4 cm. left adrenal lipid-poor adenoma. T2 weighted signal intensity is moderately hyperintense than liver. **(c)** 22 year-old-man with 1.8 cm. right adrenal pheochromocytoma. T2 weighted signal intensity is strikingly hyperintense than liver. **(d)** 64 year-old-man with 3.3 cm. right and 2.7 cm. left adrenal metastases who have a history of renal cell carcinoma. T2 weighted signal intensity of masses are moderately hyperintense than liver. **(e)** 42 year-old-woman with 9.0 cm. left adrenal ACC. T2 weighted signal intensity is seen as moderately hyperintense than liver.

FSE: Fast spin echo, ACC: Adrenocortical carcinoma.

higher than the other adrenal tumor groups. Isointense to liver is significantly higher in lipid-poor and lipid-rich adenoma groups compared to ACC, pheochromocytoma and metastasis cases. Based on malignancy, isointense to liver and slightly hyperintense than liver is found higher in benign cases whereas in malignant cases, moderately hyperintense and strikingly hyperintense than liver is higher than in benign cases ($p=0.001$, $p<0.01$) (Fig. 1a-e) (Table 2).

There was a statistically significant difference between T2 signal intensity ratio values of adrenal tumor groups ($p=0.001$, $p<0.01$). In lipid-rich and lipid-poor adenoma groups, T2 signal intensity ratio values (1.91±0.52 and 1.97±0.55, respectively) is significantly lower than pheochromocytoma (3.71±1.00) and metastases (2.80±0.72) cases ($p<0.001$). In ACC patients (4.48± 2.29) also very high mean T2 signal intensity ratio values were obtained. Pheochromocytoma and ACC patients had strikingly higher T2 signal intensity ratio values than other group tumors. T2 signal intensity ratio values of lipid-poor and lipid-rich adenomas did not differ significantly from each other ($p>0.05$). In malignant group, T2 signal intensity ratio values is found statistically significantly higher than in benign group (3.27±110 versus 1.92±0.53) ($p=0.001$, $p<0.01$) (Fig. 2a-e) (Table 2).

Qualitative CSI based on visual assessment showed that 95 out of 111 lipid-rich adenomas showed significant signal intensity loss on out of phase GE images compared to in-phase GE images reflecting high intracytoplasmic lipid content. However, 3 lipid-rich adenoma showed no signal intensity loss and 13 exhibited moderate signal intensity loss. Out of 55 patients in these lipid-rich adenoma cohort had also undergone unenhanced CT examination whose mean attenuation values were found to be less than 10 HU ensuring their high lipid content. In lipid-poor adenoma group, all of them showed no signal intensity loss. In the remaining patient cohort consisting of 17 pheochromocytomas, 3 ACCs and 24 metastases, no signal intensity loss at all was detected on opposed phase GE images compared to in phase ones reflecting absence or poor lipid content. There was a statistically significant difference between

Table 2. Evaluation of T2 weighted imaging findings according to tumor groups and malignancy

	Tumor groups												Malignancy				
	Lipid-rich adenoma (n=111)		Lipid-poor adenoma (n=31)		Metastasis (n=24)		•ACC (n=3)		Pheo (n=17)		p	Benign		Malignant		p
	n	%	n	%	n	%	n	%	n	%		n	%	n	%	
T2 visual																
Isointense to liver, lower than CSF	80	72.1	20	64.5	5	20.8	0	0	0	0	[a]0,001**	100	70.4	5	11.4	[a]0,001**
Slightly hyperintense to liver, lower than CSF	25	22.5	4	12.9	2	8.3	0	0	0	0		29	20.4	2	4.5	
Moderately hyperintense to liver, lower than CSF	6	5.4	7	22.6	11	45.8	3	100	2	11.8		13	9.2	16	36.4	
Strikingly hyperintense to liver, lower than CSF	0	0	0	0	6	25.0	0	0	15	88.2		0	0	21	47.7	
T2 SI index																
Average±SD	1.91±0.52		1.97±0.55		2.80±0.72		4.48±2.29		3.71±1.00		[b]0,001**	1,92±0.53		3,27±1.10		[c]0.001**
Median (min-max)	1.9(0.8-3.1)		1.9(1.2-3.9)		3 (1.8-4.5)		4.8(2.2-6.6)		3.6(2.2-5.6)			1,9(0.8-4)		3,1(1.8-7)		

•: Not included in the comparison due to insufficient number of observations, [a]: Fisher Freeman Halton Test, [b]: Kruskal Wallis Test, **: p<0.01. ACC: Adrenocorticalcarcinoma, Pheo: Pheochromocytoma

CSI visual assessment of adrenal tumor groups (p=0.001, p<0.01). Although moderate and significant signal intensity loss were usually detected in lipid-rich adenoma group, never detected in other tumor groups (Fig. 3a-j) (Table 3).

Quantitative CSI was carried out on the basis of Adrenal to-spleen si ratio and Adrenal si index formulas. Pheochromocytomas and metastases demonstrated significantly higher Adrenal to-spleen si ratio (1.11±0.15 and 1.04±0.20, respectively) and lower Adrenal si index values (-14.8±17.65 % and -7.50±14.47 %, respectively) than lipid-rich adenomas (0.39±0.36, 62.95±19.39 %, respectively). Lipid-poor adenomas had also similarly higher Adrenal to spleen si ratio (0.94 ± 0.31) and relatively lower Adrenal si index values (12.80± 21.03%) than lipid-rich adenomas. Adrenal ACCs had a (1.21±0.45) Adrenal to spleen si ratio and a (-1,28±2,04 %) Adrenal si index value. There was a statistically significant difference in Adrenal to spleen si ratio and Adrenal si index values between adrenal tumor groups (p=0.001, p<0.01). Lipid-rich adenomas' Adrenal to-spleen si ratio values were significantly lower but, Adrenal si index values were significantly higher than other adrenal tumor groups (p=0.001, p=0.001, p=0.001, p<0.01). There was also statistically significant difference between benign and malignant adrenal tumor groups (p=0.001, p<0.01). In malignant group, Adrenal to spleen si ratio values (1.08±0.20) were found significantly higher whereas, Adrenal si index values (-9.91±15.69 %) were significantly lower compared to benign tumors ((0.51±0.41) and (52.00±28.63%), respectively) (p=0.001, p<0.01) (Fig. 4a-j) (Table 3).

On dynamic contrast-enhanced MRI, tumor contrast enhancement patterns based on visual assessment on late-arterial phase images were categorized as follows:

6 pheochromocytomas were capillary blush, 2 were peripheral-patchy and 9 were strikingly capillary type enhancement. In ACC group, 2 ACCs had hypovascular and 1 had peripheral-patchy type enhancement. In metastases group; 13 had peripheral-patchy, 5 had homogenous, 5 had hypovascular and 1 had capillary blush-type enhancement. In lipid-poor adenoma group; 17 had capillary blush, 8 had homogenous and 5 had hypovascular and 1 had peripheral-patchy type enhancement and lipid-rich adenoma group; 29 had capillary blush, 53 had homogenous, 26 had hypovascular and 3 had peripheral-patchy type enhancement. Given this visual evaluation we can assert that adenomas mostly showed either capillary blush or homogenous type enhancement. There was a statistically significant difference on late-arterial phase visual assessment of adrenal tumor groups (p=0.001, p<0.01). In pheochromocytoma group, strikingly capillary blush enhancement is seen significantly higher than in other adrenal tumors. In ACC

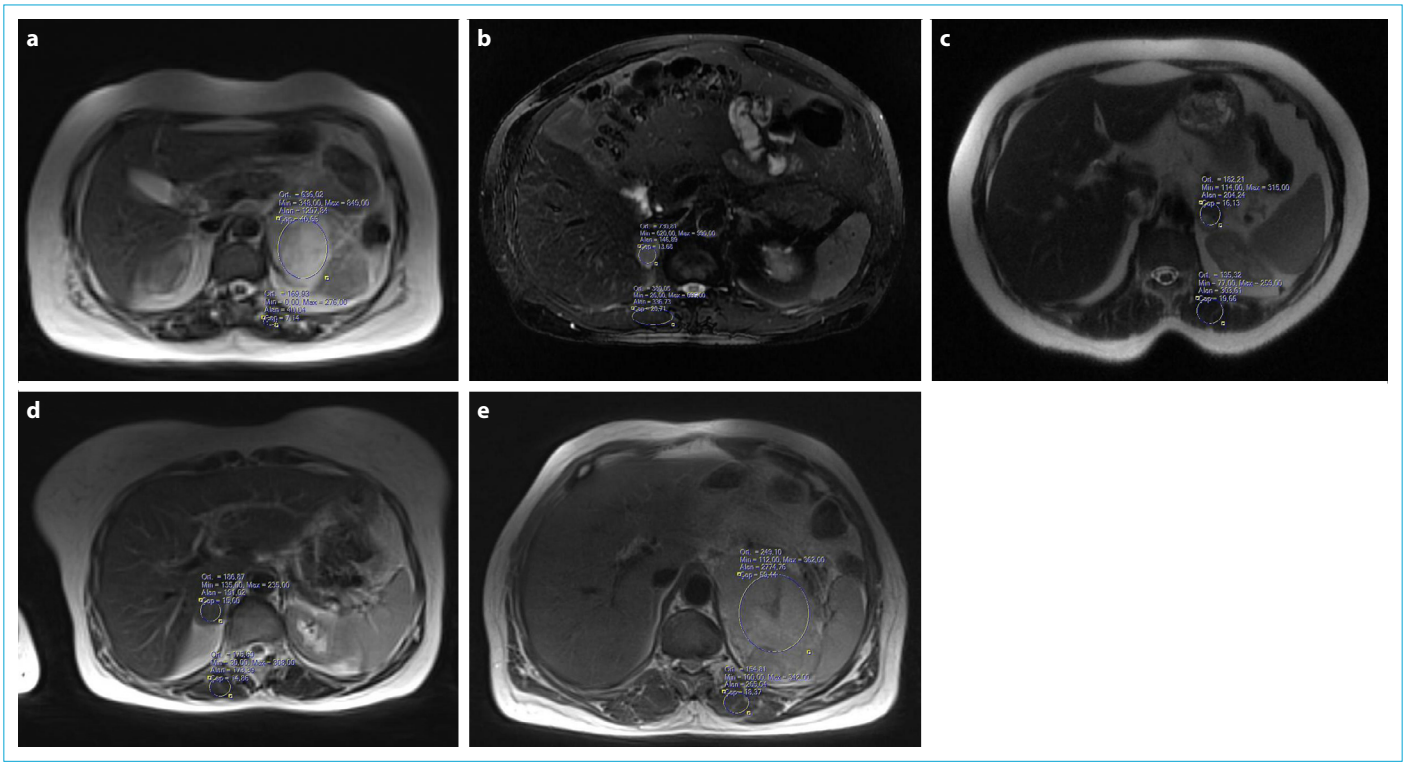

Figure 2. T2 signal intensity ratio values of different type adrenal tumors. **(a)** 54 year-old-man with 6.9 cm. left adrenal pheochromocytoma. T2 signal intensity ratio was calculated as 3.76 and strikingly higher than other type tumors. **(b)** 56 year-old-man with 2.9 cm. right adrenal metastasis. T2 signal intensity ratio was calculated as 1. and can be considered as high. **(c)** 53 year-old-woman with 2.4 cm. left adrenal lipid-poor adenoma. T2 signal intensity ratio was calculated as 1.34. **(d)** 55 year-old-woman with 3.0 cm. right adrenal lipid-rich adenoma. T2 signal intensity ratio was calculated as 1.06 which is close to the lipid-poor adenoma. **(e)** 59 year-old-man with 12.1 cm. left adrenal ACC. T2 signal intensity ratio was calculated as 1.60.

group, hypovascular type enhancement is more common than lipid-poor adenoma and pheochromocytoma group. Capillary blush-type enhancement is seen asd more common in adenomas and pheochromocytomas than in other tumor groups. Homogenous type enhancement is significantly higher in lipid-rich adenomas, lipid-poor adenomas and metastases compared to other adrenal group tumors. Peripheral-patchy type enhancement is significantly higher in metastases, compared to other adrenal tumors. Based on malignancy, there is a statistically significant difference between adrenal tumor groups (p=0.001, p<0.01). Although capillary blush and homogenous type enhancement are more common in benign cases than in malignant ones, peripheral-patchy and strikingly capillary blush type enhancement are more frequent in malignant tumors than in benign ones (Fig. 5a-n) (Table 4). On dynamic contrast-enhanced MRI, we also measured mean signal intensity of adrenal tumors on late-arterial phase images. There is a statistically significant difference between mean arterial pulse signal intensity values of adrenal tumor groups (p=0.001, p<0.01). Mean arterial signal intensity values of lipid-rich adenoma (162.85±63.13) patients are significantly lower than those of metastasis (243.18±62.25) and pheochromocytoma (295.62±90.15) patients (p=0.01, p=0.01, p<0.01). The pheochromocytoma group had significantly higher values than lipid-poor adenoma (207.27±98.66) type of tumors (p=0.015; p<0.05). Based on malignancy, mean arterial pulse signal intensity values of malignant tumors (256.8 ± 82.74) were statistically higher than benign tumors (172.55±74.3) (p=0.001; p<0.01) (Fig. 6a-e) (Table 4).

ROC analyses were performed and cut-off values were also determined for T2 si index, Adrenal to spleen si ratio, Adrenal si index and mean arterial pulse si value parameters in order to predict malignancy.

In the discrimination of benign adrenal masses from malignant ones using T2 si index, the ROC AUC value was 89.1 (95% CI: 0.837-0.945). T2 si index cut-off value of ≥2.62 showed a significant correlation in the prediction of malignancy (p=0.001, p<0.01). A T2 si index cut off value of ≥ 2.62, resulted in a 72.73% sensitivity, 90.71 % specificity, 71.1 % positive predictive value, 91.4 % negative predictive value and86.4% accuracy. We can state that risk of malignancy increased 26.05 times for a T2 si index cut-off value of ≥2.62. For adrenal to spleen si ratio, the ROC AUC

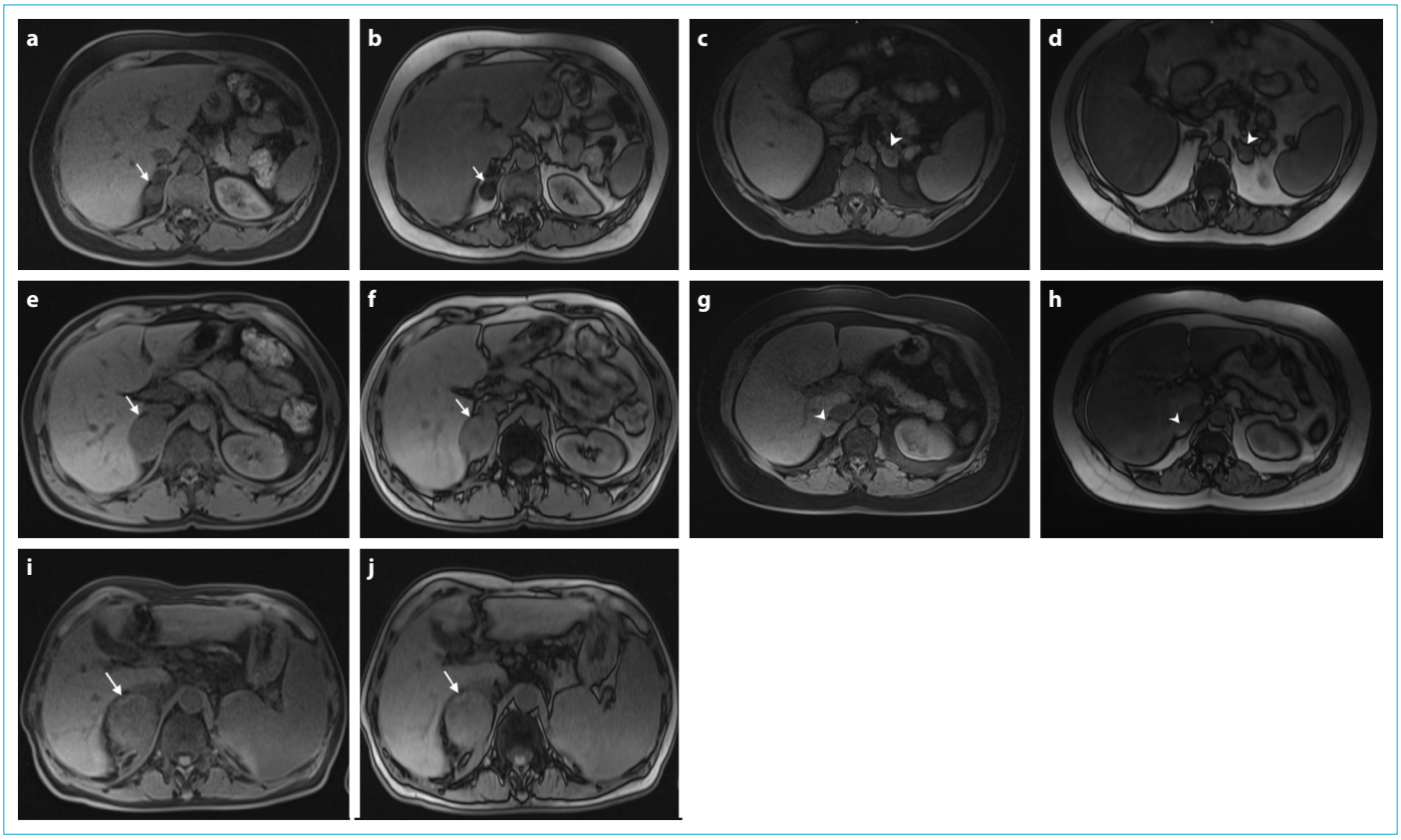

Figure 3. CSI in phase and out of phase GE images. Visual assessmentof different type adrenal tumors. **(a,b)** 52year-old-woman with 2.1 cm. and 1.2 cm. right adrenal lipid-richadenomas. There is significant signal intensity loss on opposed phase image compared to in phase image reflecting high lipid content of the lesions. **(c,d)** 53 year-old-woman with 2.4 cm. left adrenal lipid-poor adenoma. No signal intensity loss was seen on opposed phase image compared to in phase image reflecting poor or absence of lipid content in the lesion. **(e,f)** 41 year-old-man with 5.4 cm. right adrenal pheochromocytoma. No signal intensity change was found between in and opposed phase GE images. **(g,h)** 51 year-old-woman with 2.3 cm. rightadrenal metastasis. Again signal intensity difference was absent between two images. **(i,j)** 74 year-old-man with 5.2 cm.right adrenal ACC. The huge mass did not exhibit a signal intensity drop as expected.

CSI: Chemical shift imaging.

value was 93.1 (95% CI: 0.895–0.968). Adrenal to spleen si ratio value of ≥0.86 has a significant correlation in the prediction of malignancy (p=0.001, p<0.01). An adrenal to spleen si ratio cut-off value of ≥0.86 was applied, a 95.5% sensitivity, 87.3% specificity, 70% positive predictive value, 98.4% negative predictive value and a 89.2% accuracy value were obtained. We can conclude the risk of malignancy increased 144,667 times for an adrenal to spleen si ratio cut-off value of ≥0.86 was applied.

The ROC AUC value was calculated as 89.2 (95% CI: 0.838–0.947) for adrenal si index. Adrenal si index value of ≤11.6 % showed a significant correlation in the prediction of malignancy (p=0.001, p<0.01). An adrenal si index cut off value of ≤ 11.6% was used, a 100% sensitivity, 88.7% specificity, 73.3% positive predictive value, 100% negative predictive value and 91.4% accuracy values were found.

The ROC AUC value was calculated as 80.1 (95%CI: 0.732-0.871) for arterial pulse si value. Arterial pulse si value of ≥183.6 showed a significant correlation in the prediction of malignancy (p=0.001, p<0.01). An arterial pulse si cut-off value of ≥183.6 was used, a 84.09% sensitivity, 66.2% specificity, 43.5% positive predictive value, 93.1% negative predictive value and 70.4% accuracy values were found. We can conclude the risk of malignancy increased 10.35 times for an arterial pulse signal intensity cut-off value of ≥183.6 was applied (Table 5).

Discussion

Advances in imaging technology have resulted in a substantial increase in the adrenal mass detection. Accurate adrenal mass characterization is essential particularly in patients who have a known primary extra-adrenal malignancy, because this can affect patient survival and may lead to a contraindication for curative treatment.

In our study, we performed dynamic contrast-enhanced MRI including CSI and evaluated 3 qualitative and 3 quanti-

Table 3. The distribution of CSI findings of lesions according to tumor groups and malignancy

	Tumor Groups										Malignancy				
	Lipid-rich adenoma (n=111)		Lipid-poor adenoma (n=31)		Metastasis (n=24)		•ACC (n=3)		Pheo (n=17)		p	Benign		Malignant		p
	n	%	n	%	n	%	n	%	n	%		n	%	n	%	
CSI visual																
No SI loss	3	2.7	31	100	24	100	3	100	17	100	[a]0.001**	33	23.2	44	100	[a]0.001**
Moderate SI loss	13	11.7	0	0	0	0	0	0	0	0		14	9.9	0	0	
Significant SI loss	95	85.6	0	0	0	0	0	0	0	0		95	66.9	0	0	
CSI Adrenal/Spleen SI ratio																
Average±SD	0.39±0.36		0.94±0.31		1.04±0.20		1,21±0,45		1.11±0.15		[b]0.001**	0.51±0.41		1.08±0.20		[c]0.001**
Median (min-max)	0.3 (0.1-3.2)		0.9 (0.6-2.2)		1 (0.7-1.5)		1 (0.9-1.7)		1.1 (0.9-1.5)			0.4 (0.1-3.2)		1 (0.7-1.7)		
Adrenal SI index																
Average±SD	62.95±19.39		12.80±21.03		-7.50±14.47		-1.28±2.04		-14.8±17.65		[b]0.001**	52.00±28.63		-9.91±15.69		[c]0.001**
Median (min-max)	65.8 (-43-88.1)		18.5 (-63-45.6)		-1.6 (-40.8-11.6)		-2.2 (-2.7-1)		-13.5 (-58-5)			60.7 (-63-88.1)		-4.5 (-58-11.6)		

•: Not included in the comparison due to insufficient number of observations, [a]: Fisher Freeman Halton Test, [b]: Kruskal Wallis Test, **: p<0.01. CSI: Chemical shift imaging, ACC: Adrenocorticalcarcinoma, Pheo: Pheochromocytoma.

tative parameters on these images and compared obtained results in terms of adrenal mass characterization and also investigated whether we can achieve to define more indeterminate adrenal masses by combining these data.

Varghese et al.[18] investigated the diagnostic accuracy of MRI based on qualitative analysis of T2 relaxation times in the discrimination of pheochromocytomas from other adrenal masses. They could only correctly identify 11 out of 17 (65%) pheochromocytoma cases based on their long T2 relaxation times. 6 pheochromocytoma cases were misclassified due to their short T2 relaxation times. They stated this overlap as an unusual finding which has not previously been reported. In their study, they were able to correctly classify majority of the malignant lesions (83%) based on their assumed moderately hyperintense T2 signal intensity characteristics . In a study performed by Borhani and Hosseinzadeh,[19] 69 % of pheochromocytomas in their patient cohort exhibited an equal signal intensity to CSF, yielding a 69 % sensitivity and 81 % specificity in the discrimination of these masses from lipid-poor adenomas and malignant masses. We had 17 pheochromocytoma cases in which 15 of them exhibited a strikingly hyperintense and 2 were moderately hyperintense signal intensity than liver as expected. Adrenal adenomas are usually isointense or slightly hyperintense, whereas metastases and ACCs are usually moderately hyperintense to liver on T2 weighted images. In the literature, some studies showed that adenomas have lower T2 weighted signal intensity than metastases, ACCs and pheochromocytomas.[20,21] In a recently published study by Tu et al.,[22] T2 weighted signal intensity and T2 weighted entropy method could be used in combination in order to differentiate lipid-poor adenomas from metastases. This is called as "adrenal MRI calculator " which has a high accuracy in the diagnosis of lipid-poor adenoma and yet is not known its suitable for lipid-rich adenoma diagnosis. In our study, in lipid-rich and lipid-poor adenoma group, isointense to liver was significantly higher than ACC, metastasis and pheochromocytoma cases. In benign cases, isointense and slightly hyperintense to liver were more common, whereas moderately and strikingly hyperintense to liver were mostly detected in malignant group. These findings have shown a strong correlation with the literature.

Quantitative T2 signal intensity ratio has been proven to be useful in the discrimination of pheochromocytomas from adenomas. Borhani and Hosseinzadeh[19] used a T2 signal intensity ratio of at least 3.95 and obtained a 81% sensitivity and 88% specificity in the differentiation of pheochromocytomas from other adrenal masses. Similarly, Schieda et al.[20] applied a 3.80 threshold value and achieved a 100% specificity but their sensitivity decreased to 51.7% due to 36% of pheochromocytomas in

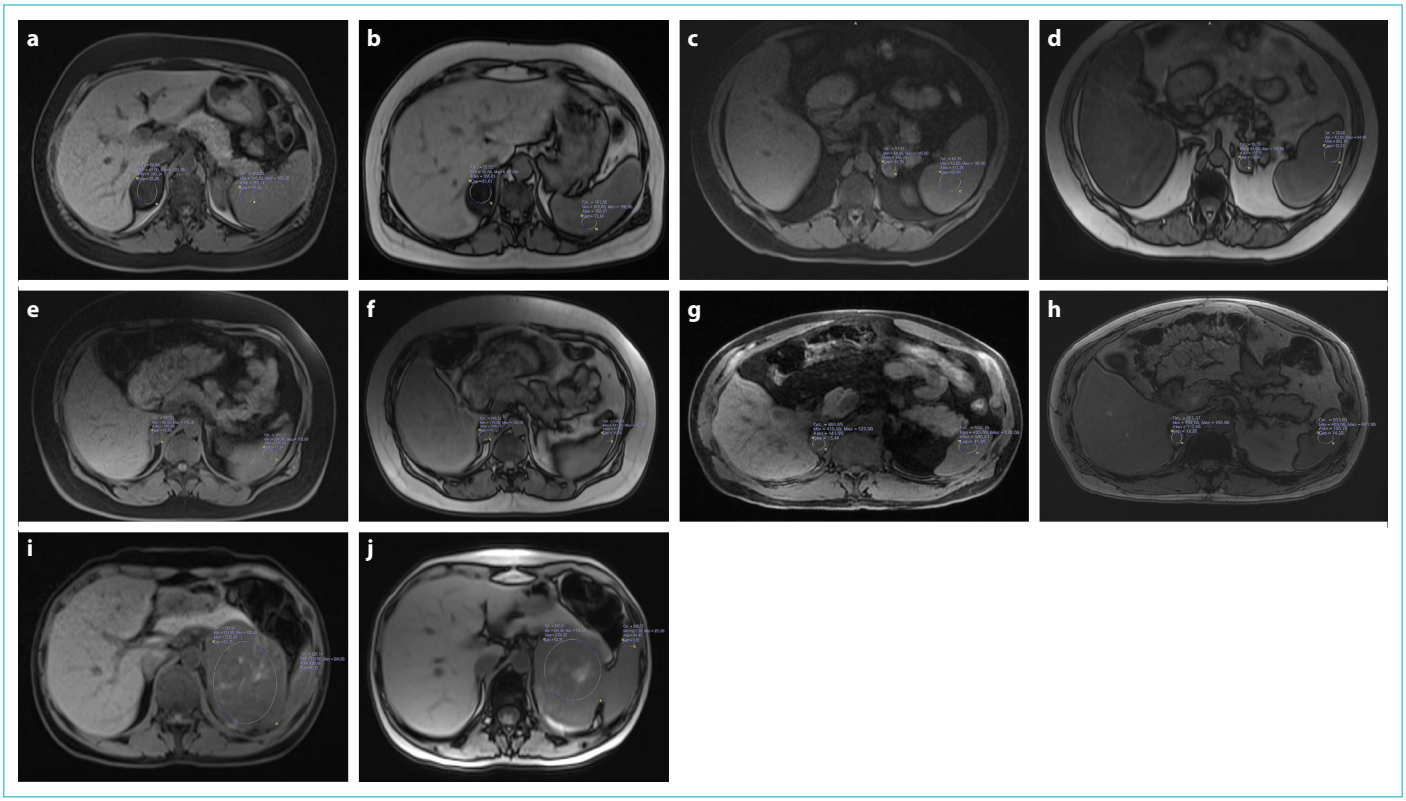

Figure 4. CSI in phase and out of phase GE images. Quantitative assessmentof different type adrenal tumors. **(a,b)** 44 year-old-woman with 4.2 cm. right adrenal lipid-richadenoma. Adrenal to spleen si ratio was calculated as 0.62 and Adrenal si index was % 30.2. **(c,d)** 55 year-old-woman with 2.4 cm.left adrenal lipid-poor adenoma. Adrenal to spleen si ratio was 1.18 and Adrenal si index was % - 8.9. **(e,f)** 40 year-old-woman with 2.0 cm.right adrenal pheochromocytoma. Adrenal to spleen si ratio and Adrenal si index were calculated as 1.35 and % - 39.8, respectively. **(g,h)** 56 year-old-man with 2.9 cm.right adrenal metastasis. 1.32 and% - 31.9 values were obtained with two formulas. **(i,j)** 42 year-old-woman with 9.0 cm.leftadrenal ACC. The huge mass did show a Adrenal to spleen si ratio of 1.45 and Adrenal si index of % - 54.8 values.

CSI: Chemical shift imaging.

their population exhibited lower T2 signal intensity ratio values. In our study, pheochromocytomas strikingly and metastases apparently showed higher T2 signal intensity ratio values than lipid-poor and lipid-rich adenomas. Apart from other studies performed in the literature, we did determine a threshold value not only for differentiation of pheochromocytomas, instead of serving as a landmark in the benign versus malignant discrimination. We applied a threshold value of ≥2.62 in order to predict malignancy and obtained fairly satisfactory results of a 73% sensitivity, 91% specificity and a 86% accuracy. Most of the lipid-rich adenomas in our patient cohort exhibited significant signal intensity loss however, a relatively small group of patients showed moderately signal loss. Only three adenomas did not show signal loss. But other adrenal tumors did not exhibit signal intensity loss on out of phase images depending on their absent or poor lipid content. Metastatic lesions especially from clear cell renal cell carcinoma and hepatocellular carcinoma may show moderate signal intensity loss on out of phase images. Because these tumors may have lipid content and therefore may cause lipid metastases elsewhere in the body.[23,24]

Rodacki et al.[11] in their study compared visual assessment and adrenal signal intensity index formula using a cut-off value of 16.5 % parameters on CSI in the discrimination of adenomas from metastases. They stated that neither of these parameters showed a remarkable superiority to the other, but visual assessment showed a little bit greater ability in the adenoma versus metastasis discrimination compared to did ROI measurements.

The Adrenal to spleen si ratio and Adrenal si index formulas which apply widely accepted threshold values of <0.71 and >16.5 %, respectively, are highly accurate for adenoma diagnosis.[25,26] Adrenal si index is regarded as more accurate than adrenal to spleen si ratio for adenoma diagnosis.[26] There are several studies in the literature using a lower adrenal si index cut-off values for adenoma diagnosis.[27] In our study, concordant with the literature, we found significantly lower adrenal to-spleen si ratio and significantly higher adrenal si index values for lipid-rich

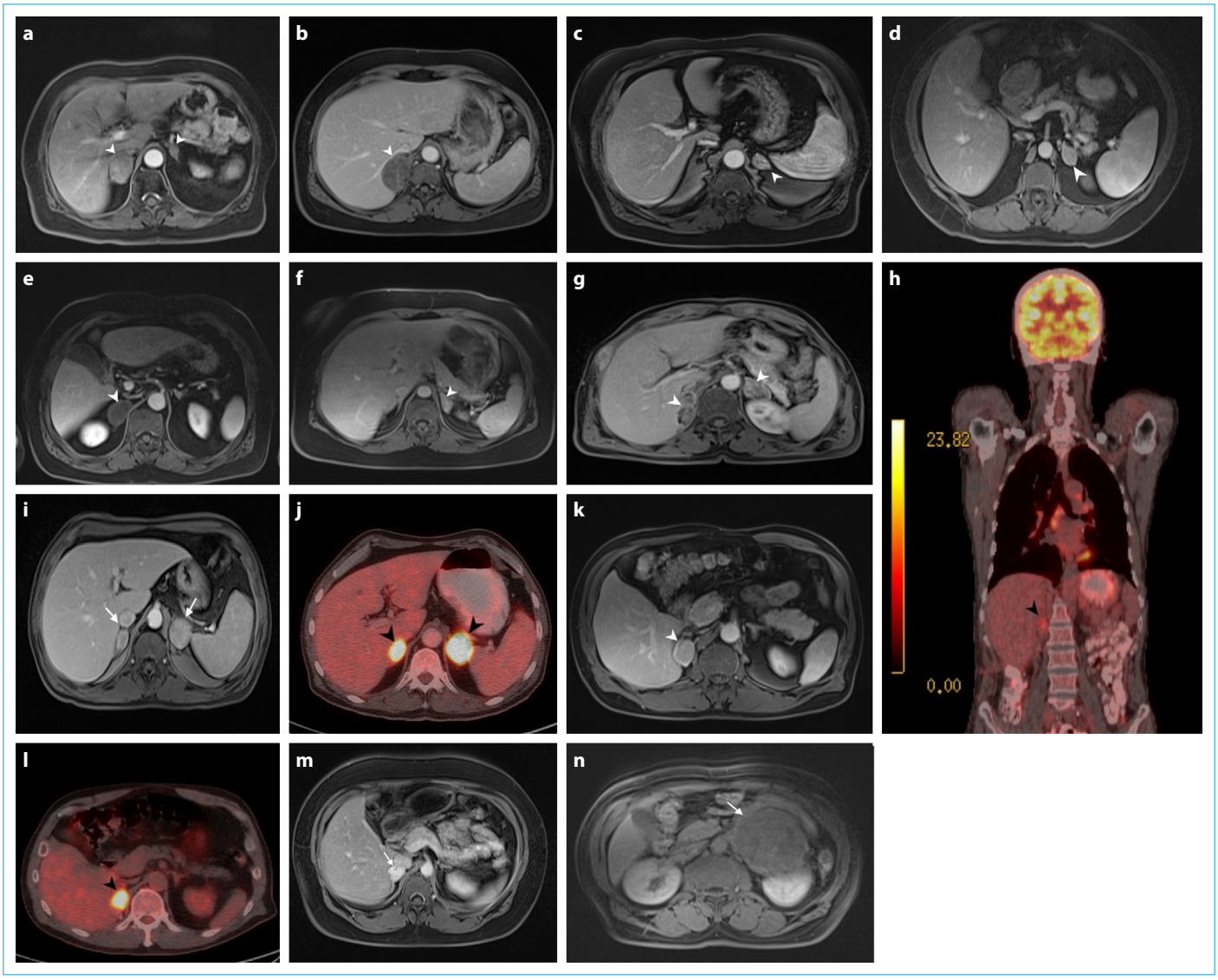

Figure 5. Dynamic contrast-enhanced 70 second 3D T1 weighted images. Visual assessment of different type adrenal tumors. **(a-c)** 66 year-old-woman with bilateral, 39 year-old woman with right and 61 year-old-man with left adrenal lipid-rich adenomas. Visual assessment reveals a bilateral homogenous, hypovascular and capillary blush type enhancement patterns,respectively. **(d-f)** 52 year-old-woman with 2.4 cm. left adrenal lipid-poor adenoma showing capillary blush type enhancement, a 72 year-old-woman with right adrenal lipid-poor adenoma had a hypovascular type contrast enhancement pattern and 69 year-old- woman with left adrenal lipid-poor adenoma exhibiting homogenous type enhancement, respectively. **(g,h)** 64 year-old-man with bilateral adrenal metastasis from renal cell carcinoma. A bilateral peripheral-patchy type enhancement patern is detected. PET-CT reveals high FDG uptake. **(i,j)** 57 year-old-man have a lung carcinoma history presenting with bilateral adrenal metastasis. A bilateral homogenous type enhancement is seen. PET-CT again shows bilateral high FDG uptake. **(k,l)** 56 year-old-man with right adrenal metastasis from renal cell carcinoma. A capillary blush type enhancement is detected. PET-CT confirms the metastasis. **(m)** 35 year-old-woman with 2.0 cm. right adrenal pheochromocytoma. A strikingly capillary blush type enhancement pattern is seen. **(n)** 59 year-old-man with 12.1 cm. left adrenal ACC. As a common feature seen in these tumors, hypovascular type enhancement is present.

PET-CT: 18F-Fluorodeoxyglucose Positron Emission Tomography. FDG: Fuorine- 18-fludeoxyglucose, ACC: Adrenocortical carcinoma.

adenoma cases compared to other adrenal tumors. For discrimination of benign versus malignant adrenal tumors, we applied threshold values of ≥0.86 and ≤11.6% for adrenal to spleen si ratio and adrenal si index, respectively. Thus, we obtained a 95.5% sensitivity, 87.3% specificity and 89.2% accuracy for adrenal to spleen si ratio and 100% sensitivity, 88.7% specificity and 91.4% accuracy for adrenal si index. As mentioned by some studies, we also obtainedslightly better results for the latter formula. We assume that these threshold values could be applied in the daily radiology practice, but need future studies including larger patient cohorts for validation.

Table 4. The distribution of contrast-enhanced MRI findings of lesions according to tumor groups and malignancy

	Tumor Groups										Malignancy				
	Lipid-rich adenoma (n=111)		Lipid-poor adenoma (n=31)		Metastasis (n=24)		ACC (n=3)		Pheo (n=17)		p	Benign		Malignant		p
	n	%	n	%	n	%	n	%	n	%		n	%	n	%	
Arterial visual																
Capillary blush	29	26,1	17	54,8	1	4,2	0	0	6	35,3	[a]0,001**	46	31,4	7	15,9	[a]0,001**
Homogenous	53	47,7	8	25,8	5	20,8	0	0	0	0		61	43,0	5	11,4	
Hypovascular	26	23,4	5	16,1	5	20,8	2	66,7	0	0		31	21,8	7	15,9	
Patchy& peripheral	3	2,7	1	3,2	13	54,2	1	33,3	2	11,8		4	2,8	16	36,4	
Strikingly capillary blush	0	0	0	0	0	0	0	0	9	52,9		0	0	9	20,5	
Arterial pulse SI																
Average±SD	162,85±63,13		207,27±98,66		243,18±62,25		145,80±64,00		295,62±90,15		[b]0,001**	172,55±74,3		256,8±82,74		[c]0,001**
Median (min-max)	150,6 (54,2-379)		190,9(48-495)		240 (153-357,6)		176 (72,3-189)		285 (166-547)			157 (48-495)		247 (72-547)		

•: Not included in the comparison due to insufficient number of observations, [a]: Fisher Freeman Halton Test, [b]: Kruskal Wallis Test, **: p<0.01. ACC: Adrenocorticalcarcinoma, Pheo: Pheochromocytoma

In the literature, there are a few studies describing enhancement patterns of adrenal tumors on dynamic gadolinium-enhanced MRI.[28,29] Rodacki et al.[11] in their study showed that enhancement pattern of adrenal adenomas largely differs from those of malignant tumors in which adenomas usually exhibit either a capillary blush or homogenous type enhancement, whereas malignant tumors mostly have a peripheral type enhancement on early-arterial phase gadolinium images. In patient cohort of Chung et al.,[28] 71% of adenomas exhibited a homogenous capillary blush, but remaining 29 % of adenomas had a heterogenous capillary blush which is mostly concordant with the previous study. In our study, similar to mentioned studies, adenomas mostly showed either a capillar blush or homogenous type enhancement pattern. Peripheral-patchy type enhancement pattern was significantly higher in metastasis patients. In pheochromocytoma patients, strikingly capillary blush-type enhancement was usually encountered. Based on malignancy, capillary blush and homogenous type enhancement patterns are common in benign adrenal tumors, whereas in malignant ones, strikingly capillary blush and peripheral-patchy type enhancement patterns are mostly seen.

Several studies have been performed on dynamic contrast-enhanced CT and MRI measuring mean signal intensity of adrenal masses on different phases. Northcutt et al.[30] established a dual-phase CT enhancement protocol to differentiate adrenal adenomas from metastases. No adenoma exhibited more than 85 HU enhancement during the arterial phase and 85% of them showed greater enhancement during the venous phase. In arterial phase, 58% pheochromocytomas exhibited a more than 110 HU enhancement. They concluded that a mass showing intense enhancement on the arterial phase strongly favors a pheochromocytoma rather than an adenoma which usually enhances on venous phase rather than arterial phase. Schieda et al.[20] in their study revealed that although mean peak CT enhancement of pheochromocytomas on 70-second images was higher than those of adenomas, a threshold level could not be determined due to substantial overlap between two groups. In the patient cohort of Rodacki et al.,[11] adenomas showed greater enhancement during the arterial phase, whereas pheochromocytomas and metastases exhibited peak enhancement on the interstisiel phase images. Conversely, our study showed that pheochromocytomas and metastases showed greater mean late-arterial phase signal intensity enhancement values than did lipid-poor and lipid-rich adenoma group which the latter one had the lowest enhancement values.

In our study, we used qualitative parameters for adrenal mass characterization and we think these assessments

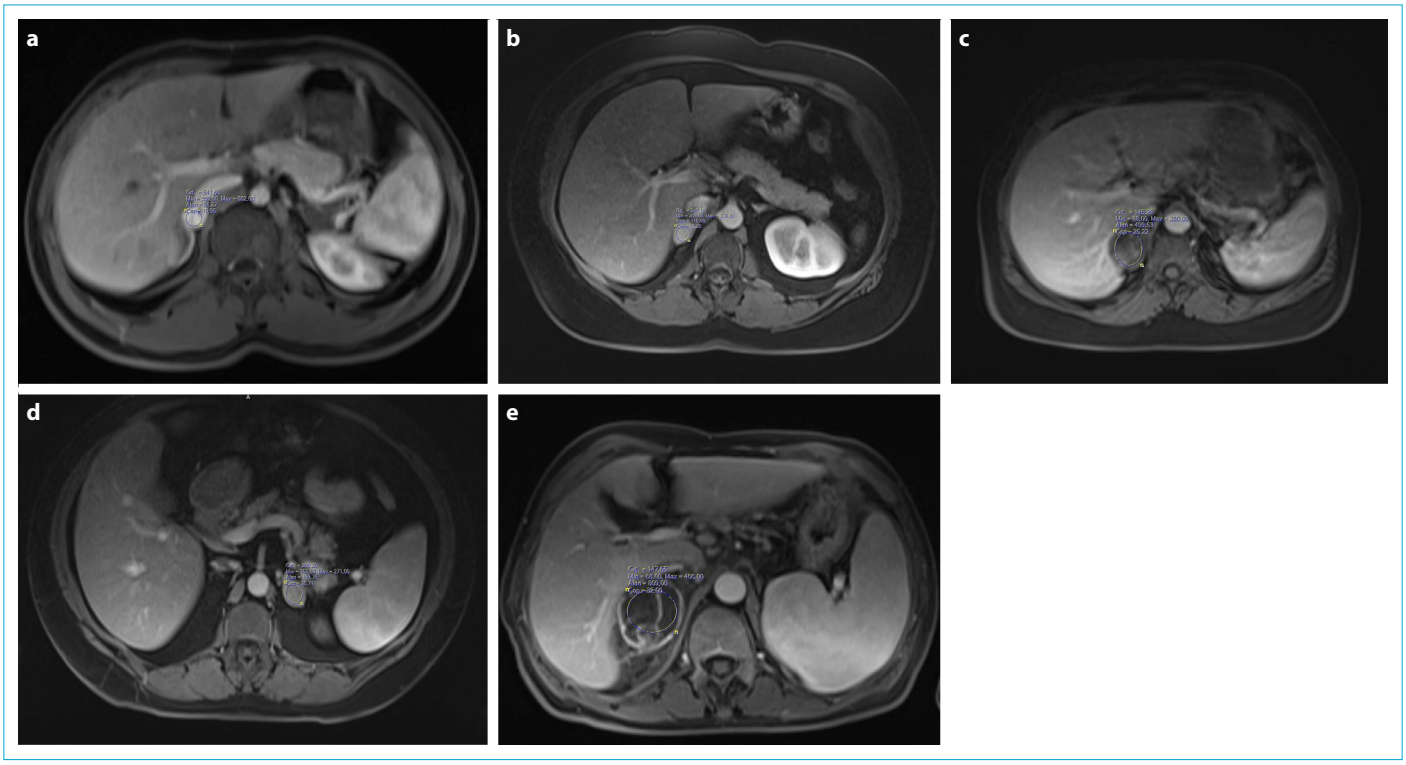

Figure 6. Dynamic contrast-enhanced 70 second 3D T1 weighted images. Quantitative assessment of different type adrenal tumors. **(a)** 22 year-old-man with 1.8 cm. right adrenal pheochromocytoma. A signal intensity value of 541.68 was measured. **(b)** 51 year-old-woman with 2.3 cm. right adrenal metastasis. Signal intensity value of 240.10 obtained. **(c)** 44 year-old-woman with 4.2 cm. right adrenal lipid-rich adenoma with a signal intensity value of 145.26. **(d)** 55 year-old-woman with 2.4 cm. left adrenal lipid-poor adenoma. 205.20 value was obtained. **(e)** 74 year-old-man with 5.2 cm. right adrenal ACC. A signal intensity value of 147.65 was obtained from the most enhancing portion of the tumor.

ACC: Adrenocortical carcinoma.

strongly supported the power of the study. Because qualitative analysis is more convenient in the everday radiology practice than quantitative analysis. Besides, it is much less influenced by artifacts, magnetic field inhomogeneities and partial volume effects etc. compared to the quantitative analysis. But, our study has several limitations. First, it is a single-center retrospective study and this design may lead to a selection bias in the studied patient cohort. Second, we do not have pathologic proof for adenoma diagnosis and instead of used a follow-up imaging protocol confirming stability of masses during at least one-year time period. Third, our sample size for malignant adrenal tumors is relatively small. Fourth, we did not include adrenal masses of less than 1 cm in the study and therefore obtained results can not be applied to smaller masses. Finally, we determined some new threshold values for quantitative MR imaging and we think they may be applicable on daily radiology practice however, these values should be validated on future research studies including larger patient populations.

Table 5. Diagnostic scan tests and ROC curve findings according to T2 si index, Adrenal to spleen si ratio, Adrenal si index and Arterial pulse signal intensity

	Diagnostic scan					ROC curve		
	Cut-off	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area	95% confidence interval	p
T2 SI index	≥2.62	72.73	90.71	71.1	91.4	89.1	0.837-0.945	0.001**
Adrenal/Spleen SI ratio	≥0.86	95.45	87.32	70.0	98.4	93.1	0.895-0.968	0.001**
Adrenal SI index	≤11.60	100	88.73	73.3	100.0	89.2	0.838-0.947	0.001**
Arterial pulse SI	≥183.6	84.09	66.20	43.5	93.1	80.1	0.732-0.871	0.001**

ROC: Receiver operating characteristic.

Conclusion

We can say that a single dynamic contrast- enhanced MRI protocol including CSI is a very useful modality in the discrimination of benign versus malignant adrenal masses. Although it is a single study and does not lead to time-consuming much, by spending a relatively short time, we can perform simultaneously three qualitative and also three quantitative evaluations on these images. Thus, by combining these obtained comprehensive data, we can claim that more adrenal tumors could be recognized with greater accuracy than the other methods used for adrenal tumor characterization.

Disclosures

Ethics Committee Approval: The study was approved by the Sisli Hamidiye Etfal Training and Research Hospital Ethics Committee (No: 1997, Date: 22.02.2022).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – A.M.H.; Design – A.M.H., B.V.B.; Supervision – A.M.H.; Materials – A.M.H., B.M.; Data collection and/or processing – Y.A., B.M.; Analysis and/or interpretation – A.M.H.; Literature search – A.M.H., B.V.B.; Writing – A.M.H.; Critical review – A.M.H.

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