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Value of MRI in differentiating adrenal masses: Quantitative analysis of tumor signal intensity

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Summary

Background: Several reports show that MR imaging, especially using the chemical-shift sequence, provides highly reliable differentiation of adrenal adenomas from non-adenomas. The aim of the study was to evaluate the ability of MRI to distinguish adenomas from other adrenal masses using quantitative analysis of the tumors' signal intensity.

Material/Methods: Fifty-four patients with 57 adrenal masses underwent MRI. The tumors were determined during surgery as pheochromocytomas (8), metastases (5), adrenal cortical carcinoma (1), and adenomas (24). Nineteen masses were diagnosed as adenomas on the basis of stability on imaging follow-up and the absence of clinical and endocrinological dysfunction. Chemical-shift-weighted images (T1TFE sequence) and T2-weighted images (TSE sequence) were used for quantitative analysis which included the T2 index (adrenal mass SI to liver SI ratio) and the CSI ratio (the adrenal mass SI on the in-phase image minus the adrenal mass SI on the opposed-phase image divided by the adrenal mass SI on the in-phase image). Statistical analysis was performed with the Mann-Whitney *U* test. Receiver operating characteristic (ROC) analysis of the calculated parameters was performed.

Results: Significant differences in T2 index between adenomas (mean: 1.43±0.50) and pheochromocytomas (2.66±0.67) as well as between metastases (1.64±0.22) and pheochromocytomas were noted ($p<0.05$). The Mann-Whitney *U* test revealed no significant difference in T2 index for adenomas vs. metastases ($p=0.1$). The CSI ratio was significantly different for adenomas (0.36±0.18) vs. pheochromocytomas (-0.15±0.16) as well as for adenomas vs. metastases (-0.23±0.26). No significant difference occurred in the CSI ratios between pheochromocytomas and metastases. ROC analysis showed that the discriminatory ability of adenoma diagnosis with the CSI ratio is better than with the T2 index (areas under the ROC curve: 0.980 vs. 0.867).

Conclusions: Quantitative methods using signal intensity ratios and indexes calculated from MR images are helpful in differentiating adrenal adenomas from non-adenomas. In the presented investigation the CSI ratio appeared much more reliable than the T2 index as a quantitative means of distinguishing adenomas from other adrenal tumors.

Key words: **adrenal masses • magnetic resonance • chemical shift imaging**

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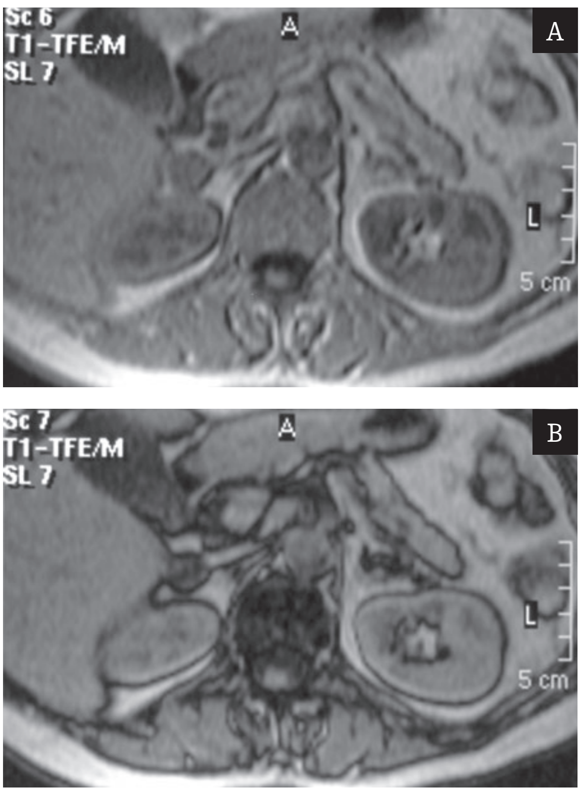
Background

Adrenal masses are found in 2-8% of routine autopsy specimens, but in the group of oncologic patients, specimens reveal adrenal lesions even in 25% of cases [1, 2]. The majority of adrenal tumors are asymptomatic adenomas and are therefore usually detected incidentally during abdominal CT or USG. The distinction between benign and malignant adrenal tumors is crucial especially in patients with a known extra-adrenal primary malignancy in which approximately half of the discovered adrenal masses are adenomas. Worth mentioning is the phenomenon of adrenal collision tumors, defined as two adjacent but histologically distinct masses [3]. Most adrenal tumors (about 70%) contain large amounts of intracellular lipid. This feature enables distinguishing typical adenomas from malignant tumors on CT and MR images [4, 5]. Unenhanced CT scans revealing attenuation values of less than 10 HU are widely accepted as confirmation of lipid-rich adenomas [6, 7]. Lipid-poor adenomas require analysis of contrast media wash-out characteristics on delayed enhanced CT scans [7-10].

Before the introduction of chemical-shift MR imaging, the signal intensities of adrenal tumors were evaluated in comparison with reference organs (mainly the liver) on T2-weighted images, and a hyperintense signal was noted for most malignant adrenal tumors as well as for atypical adenomas [11]. In the early 1990s, MR chemical-shift imaging was introduced to clinical practice. In this technique the signal intensity generated from water and lipid protons is additive on in-phase chemical-shift images and is subtractive on opposed-phase images. Chemical-shift imaging provides highly reliable differentiation of adrenal adenomas from non-adenomas based on signal loss of lipid-rich adenomas on opposed-phase images [12-19]. In cases of atypical adenomas, rapid contrast media wash-out is observed in dynamic gadolinium-enhanced MR imaging [20-23]. In radiological practice, qualitative analysis of the signal intensity on chemical-shift images is more widely performed than the quantitative approach. Nevertheless, a visual analysis of opposed-phase versus in-phase images is not always a reliable tool to confirm the signal intensity decrease in adrenal mass. The aim of the study was to evaluate the ability of MR imaging to distinguish adenomas from other adrenal masses using quantitative analysis of tumor signal intensity on chemical-shift-weighted images and T2-weighted images.



Materials and methods

The study included MR examinations of 54 patients (39 females and 15 males, age range: 21-89 years, mean: 50 years) with 57 adrenal masses. The tumors were surgically determined as pheochromocytoma in 8 cases, metastasis in 5 (4 derived from lung carcinoma, 1 from renal carcinoma), cortical carcinoma in 1, and adenoma in 24 cases. On the basis of stability on imaging follow-up (at least one year of radiological observation) and the absence of clinical and endocrinological dysfunction, 19 masses were diagnosed as adenomas. Laboratory tests revealed that only 3 of the adenomas (of a total of 43) as well as all pheochromocytomas were hyperfunctioning.

MR examinations were carried out in all patients with a 0.5 T scanner (Gyroscan T5NT, Phillips) using the chemical-shift T1TFE sequence. The axial chemical-shift images included in-phase images (TR: 15 ms, TE: 15 ms, flip angle (FA): 25°, number of signal averages (NSA): 4, field of view (FOV): 375 mm, slice thickness (THK): 7 mm, intersection gap: 0.7 mm, matrix: 256 x 256, scan time: 1:30) and opposed-phase images (TE: 6.9 ms, the other parameters the same as those above). Additionally, the protocol contained the sequences: T2TSE (TR: 2500 ms, TE: 100 ms, NSA: 6, FOV: 400 mm, TSE factor: 31, THK: 4 mm, gap: 0.4 mm, matrix: 256 x 256, scan time: 2:40, axial and coronal imaging plane) and T1SE (TR: 500 ms, TE: 15 ms, NSA: 4, FOV: 400 mm, THK: 5 mm, gap: 0.5 mm, matrix: 256 x 256, scan time: 5:10, axial and coronal imaging plane). Body and surface coil (Body Wrap Around) were used.

Quantitative analysis of the adrenal tumors' signal intensity (SI) on chemical-shift-weighted images as well as on T2-weighted images (T2TSE sequence) was performed. The following parameters were assessed: T2 index, defined as the adrenal mass SI divided by the liver SI, and the chemical-shift imaging (CSI) ratio, calculated as the adrenal mass SI on the in-phase image minus the adrenal mass SI on the

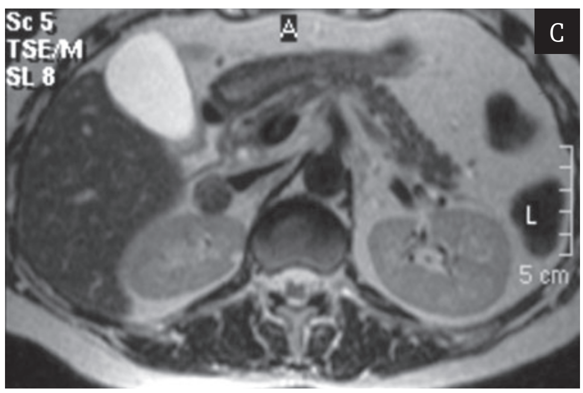
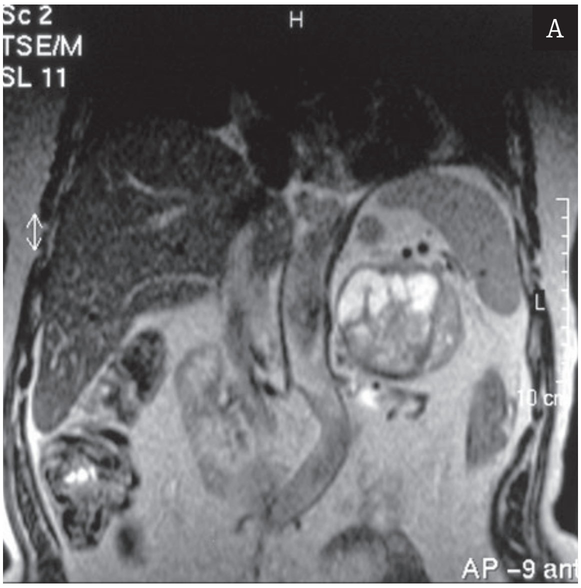
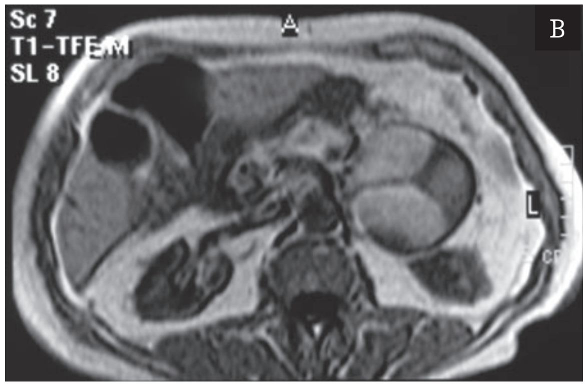


Figure 1. 45-year-old patient with right-sided surgically confirmed adrenal adenoma. **A.** On in-phase image the adrenal mass presents a homogeneous signal intensity (SI: 303). **B.** The opposed-phase image shows a lower signal intensity (SI: 213) compared with the in-phase image; however, the suppression is slightly heterogeneous; CSI ratio: 0.29. **C.** Transverse T2-weigted image shows the adrenal tumor as isointense to the liver (adrenal mass SI: 235, liver SI: 251); T2 index: 0.94.





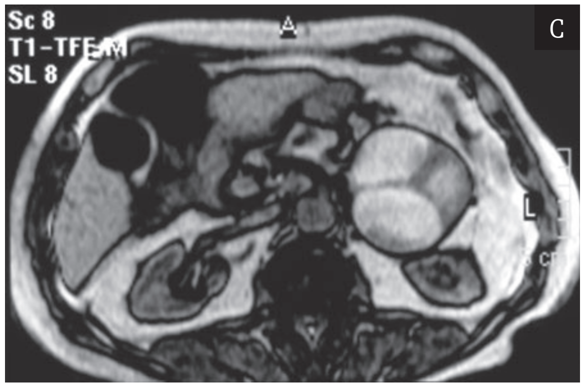


Figure 2. 55-year-old woman with left adrenal pheochromocytoma **A.** Coronal T2-weighted image depicts heterogeneous mass in the left adrenal gland (adrenal mass SI: 1203, liver SI: 402); T2 index: 2.99. **B.** The in-phase image reveals hypo- and hyperintense components within the tumor (SI: 724). **C.** On the opposed-phase image, no drop in signal intensity is visible (SI: 1019); CSI ratio: -0.40.

opposed-phase image divided by the adrenal mass SI on the in-phase image. Signal intensities of the adrenal lesions and reference tissue (liver parenchyma) were measured on the same slice with an electronic cursor using a circular region of interest (ROI). An ROI as large as possible was placed within the adrenal mass on chemical-shift and T2-weighted images (excluding the area of necrosis and hemorrhage and avoiding the edge of the lesions) as well as in the liver (T2-weighted images). Only adrenal tumors with diameters exceeding 10 mm were evaluated. The calculations were done by a single investigator who was unaware of the clinical data.

The Mann-Whitney *U* test was used for statistical analysis. A value of $p<0.05$ was regarded as statistically significant. The calculated values of the T2 index and CSI ratio were compared in three groups of adrenal tumors (established on the basis of the histopathological or clinical diagnosis), i.e. adenomas (Fig. 1A-C), pheochromocytomas (Fig. 2 A-C), and metastases (Fig. 3 A-C). Receiver operating characteristic (ROC) curves were constructed to evaluate the discriminatory abilities of the analyzed parameters [24, 25].

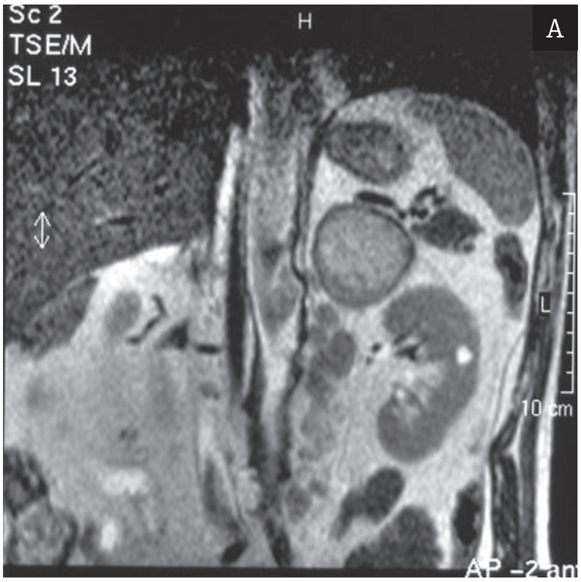
Results

Analysis of T2-weighted images

In the analyzed group of 57 adrenal masses, we noted slightly or considerable higher signal intensity relative to the liver parenchyma in 47 tumors (82.5%). For the adenomas (n=43) the mean T2 index was 1.43±0.50 (range: 0.623-30). The respective values for the pheochromocytomas (n=8) were 2.66±0.67 (range: 1.93-3.94). In the group of metastatic tumors (n=5) the mean T2 index was calculated as 1.64±0.22 (range: 1.44-1.95). For all 14 non-adenomas (pheochromocytomas, metastases, and a single case of cortical carcinoma) the mean T2 index was 2.30±0.72 (range: 1.44-3.94). Significant differences in T2 index between adenomas and pheochromocytomas as well as between metastases and pheochromocytomas were noted ($p<0.05$). The Mann Whitney *U* test revealed no significant difference in T2 indexes for adenomas versus metastases ($p=0.1$). Figure 4 shows a scatterplot of the T2 indexes for adrenal adenomas, pheochromocytomas, and metastases. The ROC curve of the analyzed procedure (discrimination of adenomas from non-adenomas with the use of the T2 index) is presented in Figure 5. The area under the ROC curve was 0.867. For a cut-off level of 1.9 the sensitivity of the test was 84% and the specificity 71%.

Analysis of chemical-shift images

Except for two cases, adrenal adenomas presented a variable decrease in signal intensity on opposed-phase images. The mean CSI ratio for this group was 0.36±0.18 (range: -0.25 to +0.65). The respective results for pheochromocytomas were -0.15±0.16 (range: -0.41 to -0.01) and for metastases the mean CSI ratio was calculated as -0.23±0.26 (range: -0.66 to +0.03). In the group of non-adenomas, no decrease in signal intensity on the chemical-shift images was noted (mean CSI ratio: -0.20±0.19) except for one metastatic tumor. The Mann-Whitney *U* test revealed significant differences in the CSI ratios for adenomas versus pheochromocytomas as well as for adenomas versus metastases. No significant difference occurred in the CSI ratios between pheochromocytomas and metastases ($p=0.66$). The scatterplot presented in Figure 6 illustrates the distribution of the CSI ratios for the groups of adrenal lesions. The ROC curve for the diagnosis of adenomas using the CSI ratio



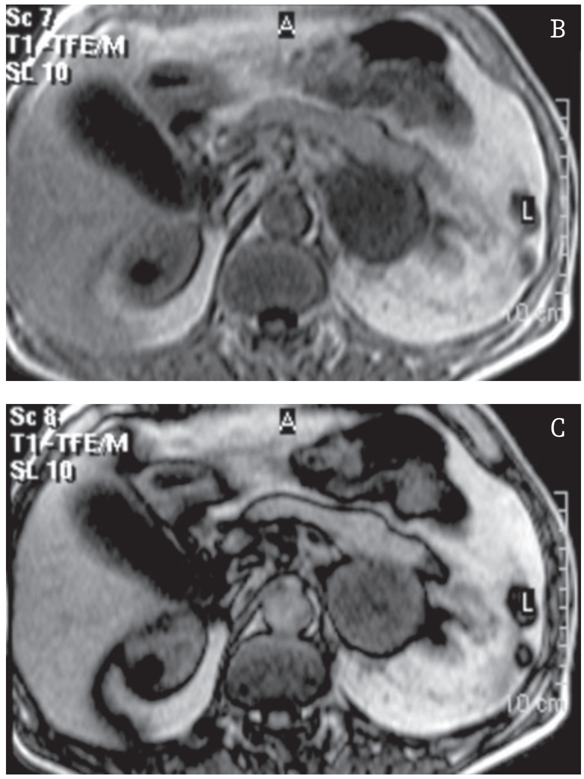


Figure 3. Male-patient aged 65 with left adrenal metastasis from lung carcinoma. **A.** Coronal T2-weighted image reveals large hyperintense tumor in the left adrenal gland as well as the lymph nodes along the aorta (adrenal mass SI: 878, liver SI: 485); T2 index 1.81. **B.** In-phase image demonstrates a hypointense adrenal tumor (SI: 324). **C.** Opposed-phase image does not show suppression of signal within the lesion (SI: 397) compared with the in-phase image; CSI ratio: -0.23.

is shown in Figure 7. The area under this ROC curve was 0.980. For a CSI ratio cut-off level of 0.031 the sensitivity of the test was 95% and the specificity 100%.

Discussion

The imaging characterization of adrenal masses has been a major focus of MR research for many years. Before MR chemical-shift imaging was introduced, investigators analyzed the signal intensities of adrenal tumors relative to that of the liver parenchyma using T2-weighted images. They reported that malignant adrenal lesions tend to present higher signal intensity on conventional T2-weighted images than adenomas, although there is a substantial overlap in signal intensities between these two groups [11, 26]. Several reports presented cases of degenerated adenomas appearing as heterogeneous, mostly hyperintense masses on T2-weighted images because of necrotic or hemorrhagic components [27-29]. For quantitative assessment, some authors calculated T2 relaxation times of adrenal lesions [30, 31], while others used the T2 index, defined as the ratio of the adrenal mass SI to the liver SI [21, 32, 33]. In our study the T2 index presented statistically significant difference between adenomas and pheochromocytomas as well as between metastases and pheochromocytomas. The mean T2 indexes for adenomas, pheochromocytmomas, metastases, and all malignant adrenal tumors in our material were 1.43, 2.66, 1.64, and 2.30, respectively. In a report by Slapa et al. [33] the mean values of the T2 index for non-hyperfunctioning adenomas, pheochromocytmomas, and malignant adrenal masses were 1.70, 3.32, and 3.06, respectively. Mitchell et al. [32] presented values of the mean T2 index for adenomas and for malignant lesions of 2.30 and 2.70, whereas the results of Korobkin et al. [21] were, respectively, 1.51 and 1.93. In our material the highest mean value of the T2 index was found for pheochromocytomas, although an overlap between pheochromocytomas and other lesions was noted. These results correspond with several reports in which authors emphasize that a very high signal intensity on T2-weighted images is the most common MR appearance of pheochromocytomas ("light bulb"). However, these tumors may also be visible as moderately hyperintense or even hypointense lesions. For this reason the epithet "imaging chameleon" has been given to pheochromocytoma [34].

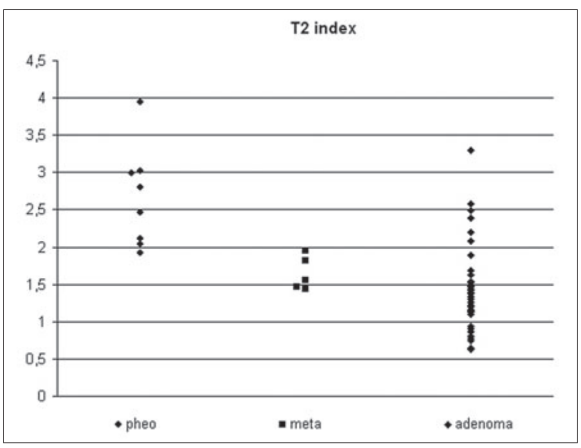


Figure 4. Scatterplot of the T2 index for the adrenal masses (adenomas, pheochromocytomas, and metastatic tumors). There are 7 overlapping cases between adenomas and pheochromocytomas, whereas considerable overlap is seen in the T2 indexes of adenomas and metastases (including all analyzed metastatic tumors). One metastasis overlaps pheochromocytomas.

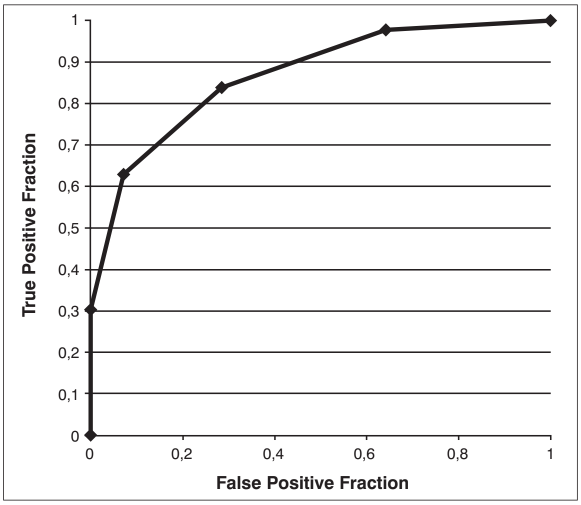


Figure 5. ROC curve for the analysis of adenomas and non-adenomas using the T2 index (ROC area: 0.867).

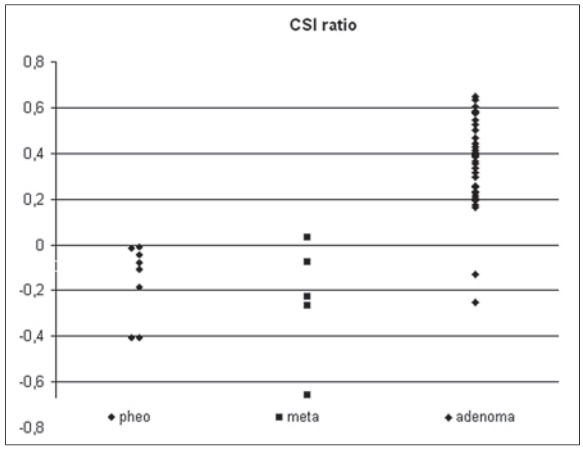


Figure 6. Scatterplot of the CSI ratio for the three groups of adrenal masses. Considerable overlap is seen between pheochromocytomas and metastases. Two adenomas overlapping pheochromocytomas as well as metastases are visible.

In the 1990s, the chemical-shift sequence was found to be useful in differentiating adrenal adenomas from non-adenomas. This sequence takes advantage of the reduced signal on opposed-phase images due to the high cytoplasmic lipid concentration in adenomas [5, 15, 27]. Visual analysis of signal intensity loss on opposed-phase images is widely performed in everyday radiological practice, but in some cases adrenal lesions demonstrate heterogeneous signal intensity suppression which is difficult to interpret [35]. Atypical signal characteristics of adrenal masses on chemical-shift images may reflect variable amounts and type of lipid cells (combination of lipid-rich and lipid-poor cells) within adenomas or come from intratumor lipid in malignant lesions (e.g. adrenal cortical carcinoma or metastases from renal cell carcinoma, hepatocellular carcinoma, or liposarcoma) [21, 33, 35]. Quantitative analysis of signal intensity alterations on chemical-shift images is recommended especially in these ambiguous cases. It is based on establishing the percentage of SI drop on opposed-phase image relative to SI on in-phase image (the SI index). The crucial point in measurements of the SI index is the methodology of ROI selection. The region of interest should be as large as possible, but without foci of necrosis, hemorrhagic components, or MR-detectable calcifications. Additionally, the investigator has to place the ROI within the tumor, avoiding its edge to eliminate partial volume artifacts at the borderline between the mass and adjacent fatty tissue. Small adrenal masses are more susceptible to partial volume effects with surrounding fat that can lead to SI decrease in the voxels at tissue boundaries. All the above-mentioned authors excluded adrenal masses smaller than 10 mm from analysis. We respected those restrictions as well.

Tsushima et al. [26] were the first to propose the SI index (CSI ratio in our report). In their study, adrenal lesions presenting SI indexes of more than 5% were adenomas and those with values of less than 5% were metastases and pheochromocytomas. In our material the minimal positive value of this parameter for 41/43 (95.4%) of the adenomas was 12% (CSI ratio: 0.12); in 2 adenomas, no SI loss was noted. In a report by Mayo-Smith et al. [36] the mean SI index in a group of 28 adenomas was 50%, whereas for 18 metastases it was 18%. In the present study the mean SI index for 43 adenomas was 36% (CSI ratio: 0.36) and for 5 metastases it was -23% (CSI ratio: -0.23; the negative value of the parameter reflects no SI drop on opposed-phase image). Slapa et al. [33] presented a mean CSI ratio of 0.27 for non-hyperfunctioning adenomas (n=36) and 0.02 for pheochromocytomas (n=27). In cases of pheochromocytomas, Slapa interpreted the small positive value of the CSI ratio as resulting from slight quantities of MR-detectable lipids. In our study the mean CSI ratio for pheochromocytomas (n=8) was -0.15. According to our results the CSI ratio appears as a parameter of the high discriminatory power in differentiating adenomas vs. non-adenomas (ROC area: 0.980). Similar results of ROC analysis were presented by Slapa (ROC area: 0.954).

Comparison of the discriminatory value of the CSI ratio for adenoma diagnosis with results presented in the cited articles is not completely appropriate due to the limitations

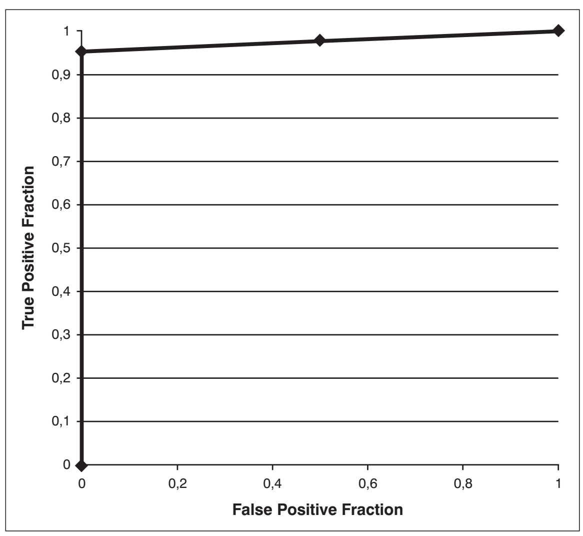


Figure 7. ROC curve for the analysis of adenomas and non-adenomas using the CSI ratio (ROC area: 0.980).

of our study. The smaller number of cases (especially of non-adenomas) in the present material is one of the factors (for comparison, Slapa reported a series of 108 adrenal tumors). The second is that the analyzed examinations were not performed with the recommended very short TE, which requires stronger MR imaging gradients than those available with our 0.5T MR unit. Several machine-dependent factors (e.g. receiver gain) render the established quantitative criteria not universal. In spite of these technical limitations, many reports seem to confirm that quantitative analysis of adrenal tumor signal intensity can fortify the conclusions based on simple visual analysis. However, further confirmatory studies using a large series of adrenal lesions should be performed before quantitative methods can be widely adopted.

Conclusions

Quantitative methods based on measurements of signal intensity on MR images are useful in differentiating adrenal adenomas from non-adenomas. In the presented investigation the CSI ratio appears much more reliable than the T2 index as a quantitative means of distinguishing adenomas from other adrenal tumors.

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