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# Proton-density fat fraction measurement: A viable quantitative biomarker for differentiating adrenal adenomas from nonadenomas

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ABSTRACT

*Purpose:* This study aims to compare the accuracy of proton-density fat fraction (PDFF) measurements with chemical shift magnetic resonance imaging (CSI) for quantifying the fat content of adrenal nodules and for differentiating adenomas from nonadenomas.
*Materials and methods:* Oil-saline phantom measurements was performed to compare the correlation between PDFF and CSI in detecting and quantifying fat content. 43 consecutive patients who had known adrenal nodules were imaged on a 3.0-T MR scanner. PDFF was measured, and the signal intensity (SI) index (SII), SI adrenal-to-liver ratio (ALR) and SI adrenal-to-spleen ratio (ASR) of the adrenal nodules were calculated.
*Results:* In the phantom study, PDFF ranged from 12.6% to 99.1% and the SII was between 0.72 and 1.23. There was good correlation between these two methods ($R$ square = 0.972, $p < 0.0001$). The PDFF of adrenal adenoma was significantly increased compared with that of nonadenoma ($p < 0.001$). PDFF was an effective tool for distinguishing adenoma from nonadenoma, with an area under the curve (AUC) of 0.98. In comparing SII, ALR and ASR the AUC was 0.94, 0.95 and 0.93, respectively. No significant difference was noted between these two methods ($p > 0.05$).
*Conclusion:* PDFF measurements provide an accurate estimation of fat content in discriminating adenomas from nonadenomas compared with CSI, avoiding complicated data calculations and offering a simpler technique using 3T.



## 1. Introduction

Adrenal nodules are common in clinical practice, and account for approximate 10% of genitourinary system tumors [1]. With the increasing utilization of abdominal and thoracic computed tomography (CT), adrenal nodules are incidentally discovered in up to 4–5% of patients [2]. Adenomas and metastases are the most common benign and malignant adrenal nodules, respectively. Pheochromocytoma is less common, and accounts for fewer than 5% of detected lesions [3]. The detection and characterization of adrenal metastases in adrenal glands are essential for accurate staging of patients with known primary tumors [4], while the pheochromocytomas could result in life-threatening hypertension or cardiac arrhythmias. In addition, 10% are considered malignant [4,5]. It is therefore important to differentiate adenomas from nonadenomas since management and outcome are very different between the 2 groups [4,6].

Adrenal adenoma often contains intracytoplasmic fat that leads to low attenuation values on unenhanced CT images. A threshold value of 20HU can result in high specificity and low sensitivity in diagnosing adrenal adenomas [7]. Shi et al. [8] demonstrated that dual-energy CT could potentially provide energy-spectrum information that would improve the accuracy of diagnosing lipid-poor adenomas without the need for intravenous contrast agents. Combing unenhanced dual-energy CT and washout rates could remarkably increase the sensitivity to 100% [9]. Lipid-poor adrenal adenomas exhibit enhancement and washout features approximately identical to lipid-rich adenomas, which significantly differ from adrenal nonadenomas [10]. On contrast-enhanced CT, a washout rate on the 15-min delayed phase is considered the most useful parameter for discriminating adenomas from nonadenomas with a threshold of 55%, due to the early inflow and outflow of contrast agent. Reported sensitivity and specificity of contrast washout was 93.9% and 95.8%, respectively, even for lipid-poor adenomas [4,6,11].

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Other contrast-enhanced techniques such as CT perfusion could quantitatively discriminate adenomas from nonadenomas with sensitivity of 76.9% and specificity of 73.2%. However, radiation exposure is concerning and widespread use of the technique is still limited [12]. Chemical-shift MRI could be used for diagnosing adrenal adenomas owing to the presence of intracytoplasmic lipid. Many adenomas lose signal intensity on opposed phase (OP) images, even with the unenhanced CT attenuation ranged between 10 and 30HU [13]. Loss of signal on OP imaging compared with in phase (IP) imaging has been proven to be highly accurate in differentiating adenomas from nonadenomas [14].

However, the calculation method for IP/OP images is relatively complicated and not intuitive. Therefore, it is essential to explore new imaging techniques which could provide high sensitivity and specificity in distinguishing between adenomas and nonadenomas, without the risk of radiation exposure or contrast agent side-effects. MRI proton-density fat fraction (PDFF) is a chemical shift iamging based water and fat separation technique. R2*(1/T2*) can be acquired in several seconds breath-hold, and the PDFF images can be used to calculate the fat fraction (FF) [15–19]. Recently, PDFF calculation became a widely used MRI biomarker for noninvasive and accurate quantification the fat content in many tissues, such as hepatic steatosis, which were compared to the golden reference of liver biopsy, and also in cases of osteoporosis [15,16,20–23]. To our knowledge, this novel technique has not been used in adrenal nodules for discriminating adenomas from nonadenomas.

The aim of our study was to compare the accuracy of PDFF measurements and conventional IP/OP images in quantifying the fat content of adrenal gland nodules and distinguishing adenomas from nonadenomas.

## 2. Materials and methods

This retrospective clinical study was approved by our Institutional Review Board and the requirement for informed consent from study patients was waived.

*Phantom study*

Prior to retrospective data collection, a prospective phantom study was performed. A soybean oil (Arianna, China)-saline (0.9%, Jiangxi KELUN, China) phantom was scanned on a 3.0 T MR scanner with a 32-channel head phased-array coil (Discovery 750, GE Medical System, Milwaukee, WI) in a bottle with mouth-up position. The phantom was allowed to settle for at least 30 min to remove the air bubbles in the oil. Three-plane positioning and a calibration sequence were performed before the examination. A three-dimensional (3D) Iterative Decomposition of water and fat with Echo asymmetry and Least Square Estimation (IDEAL-IQ) pulse sequence [20] was scanned and automatically generated PDFF maps (12 images). A 3D gradient dual echo Dixon sequence (LAVA-FLEX) was applied to generate IP, OP, water and fat images (24 images) in which a second echo acqusiton was added after the first echo[24]. The field of view (FOV) was 26 cm, slice thickness was 10 mm and location of 12 slabs was similar for both sequences. Other parameters were all similar to the clinical study and are mentioned below. The crosswise of first localization box was parallel with the oil-saline interface (Fig. 1). These two methods maintanied the same positioning, and 1 mm localization was hortizontally moved up in a parallel fashion for ten times.

*Study population*

From August 2013 to August 2014, 77 consecutive patients with adrenal nodules with or without clinical symptoms were identified. All cases were diagnosed by ultrasound (US) or CT, followed by dedicated adrenal MRI performed with our standard adrenal protocol. Inclusion criteria were: nodule size 1 cm or larger in maximum diameter, and histologic/pathologic confirmation of all adenomas and pheochromocytomas, or metastases proved by clinical history and subsequent increase in size on follow up exams. All MRI exams were performed successfully.

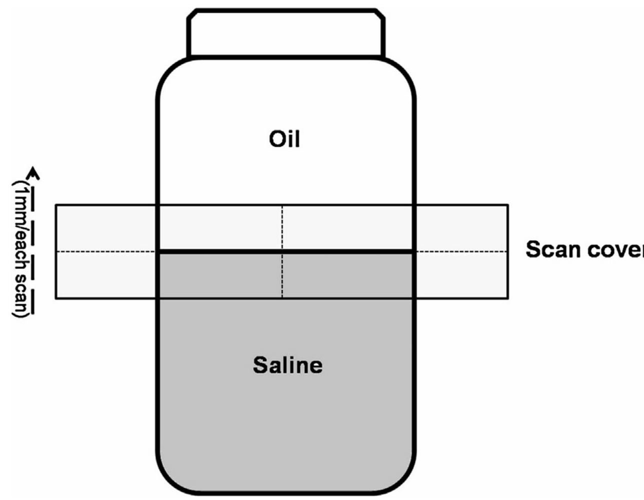


**Fig. 1.** The oil-saline phantom consisting of 50% soybean-oil and 50% saline. Data acquisition started with the interface of oil-saline boundary.

*Imaging protocol*

All 43 patients were scanned on the 3.0T MRI scanner equipped with a 32-channel torso phased-array coil (Discovery 750, GE Medical System, Milwaukee, WI) in supine position using our routine imaging protocol.

Three-plane positioning was obtained with a gradient echo sequence and a calibration sequence with a 12-s breath-hold were performed at the beginning of each examination. Conventional T2WI propeller sequence was performed. A three-dimensional (3D) IDEAL-IQ pulse sequence was scanned within a single breath-hold for 18 s and automatically generated PDFF maps at the end of sequence acquisition. Post processing was in less than 10 s. LAVA-FLEX was applied to generate IP, OP, water and fat images within a single breath-hold for 16 s.

Parameters of the IDEAL-IQ sequence were as follows: FOV 44 cm, acquisition matrix 160 × 160, number of excitation (NEX) 0.5, auto flip angle 3° was used to minimize the T1 bias, repetition time (TR) 5.9 msec, six echo with TE ranging from 0.9 to 4.5 were used to reconstruct water and triglyceride fat images, phase acceleration factor 2, echo train length (ETL) 3, bandwidth (BW) 111.11 kHz, slice thickness 4.4 mm. After image acquisition, it automatically reconstructed water, fat, IP, OP, R2* and fat-fraction maps.

Parameters of the LAVA-FLEX sequence were as follows: FOV 44 cm, acquisition matrix 260 × 224, NEX 1.0, flip angle 12°, TR 4.0 msec, two echoes with TE of 1.2 and 2.4 msec were used for each scan; phase acceleration factor 2, ETL 3, BW 142.86 kHz, slice thickness 4.0 mm. After image reconstruction, the MRI system automatically generated IP, OP, water- and fat- only images with a single breath-hold.

*Image analysis*

All clinical and phantom images were transferred to advantage workstation (AW4.5, GE Medical System, Milwaukee, WI) for post-processing. Two blinded independent experienced abdominal radiologists (five and eight years experience, for reader 1 and reader