MAJOR PAPER

Comparison of ^1H MR Spectroscopy, 3-point DIXON, and Multi-echo Gradient Echo for Measuring Hepatic Fat Fraction

Kinya ISHIZAKA¹, Noriko OYAMA^{1*}, Suzuko MITO¹, Hiroyuki SUGIMORI¹,
Mitsuhiro NAKANISHI¹, Tomoyuki OKUAKI², Hiroki SHIRATO¹, and Satoshi TERAIE¹

¹*Department of Diagnostic and Interventional Radiology, Hokkaido University Hospital
N14 W5, Kita-ku, Sapporo 060-8648, Japan*

²*Medical Satellite Yaesu Clinic*

(Received April 5, 2010; Accepted October 27, 2010)

Purpose: We evaluated and compared the reproducibility, diagnostic accuracy, and sequence dependency of the fat fraction (FF) determined by 3-point Dixon (DIXON) and multi-echo gradient-echo (MEGE) methods to those of the FF determined by magnetic resonance spectroscopy (MRS).

Methods: Our study included 98 volunteers, ten of whom underwent scanning twice to evaluate sequence reproducibility. We compared the FFs determined by the DIXON and MEGE methods to that by MRS as the gold standard, calculated sensitivity and specificity for each image analysis method at a threshold value of 6.25% of spectroscopic value, and used Pearson's correlation coefficient and Bland-Altman analysis to compare agreement among the repeated measurements and FF values with the 3 methods, in 98 volunteers.

Results: There was no significant difference in repeated scans in any sequence with Wilcoxon's t-test. Each correlation coefficient (r) exceeded 0.930 for the repeated measurements of all 3 sequences. Sensitivity of DIXON was 82% and specificity, 96%; sensitivity of MEGE was 70% and specificity, 99%. The FFs determined by DIXON and MEGE correlated well with that by MRS ($r=0.920$) but showed significant difference (paired t-test, $P<0.001$). The mean difference between the FF determined by DIXON and that by MEGE were 0.93 and -1.16 , respectively. The slope of the regression lines as determined by DIXON was -0.655 ($P<0.001$) and that by MEGE was -0.527 ($P<0.001$). When the FF by MRS was less than 6.25%, the FF values by DIXON and MEGE were significantly higher; when the spectroscopic value was greater than 6.25%, their values were significantly lower.

Conclusion: We demonstrated the high reproducibility of each FF measurement using MRS, DIXON, and MEGE. Compared to MRS, both DIXON and MEGE showed high sensitivity and specificity for determining FF. The FFs by DIXON and MEGE showed sequence dependency because DIXON had proportional and additional errors, and MEGE had a proportional error.

Keywords: *DIXON, hepatic fat fraction, multi-echo gradient echo, ^1H -MRS*

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a common chronic liver disease primarily caused by accumulation of triglycerides in hepatocytes. Fatty deposition in the liver has been associated with metabolic syndrome, and NAFLD can progress to nonalcoholic steatohepatitis (NASH), cirrhosis, and end-stage liver disease.^{1,2} NAFLD is currently

assessed by histologic visualization of hepatocellular fat vacuoles,^{3,4} but biopsy is invasive and prone to sampling error.^{5,6} A noninvasive, objective, and reproducible assessment to replace biopsy is needed in clinical settings.

Ultrasonography (US), computed tomography (CT), and magnetic resonance (MR) imaging have been used to evaluate fatty liver.⁷⁻¹⁰ US does not allow quantitative assessment of fat fraction.¹¹ In addition, with US, the threshold of the detectable fat fraction (FF) for a fatty liver exceeds 30%, which may be insufficient to detect a mildly fatty liver.¹²

*Corresponding author, Phone: +81-11-716-1161, Fax: +81-11-706-7970, E-mail: norikooyama@med.hokudai.ac.jp

CT entails radiation exposure and has problems for estimating fatty liver under iron deposition. MR imaging, on the other hand, requires no radiation exposure and is the only modality for absolute quantification of fat deposition; identification of small fat depositions is useful in diagnosing a mildly fatty liver. MR imaging has been used in place of biopsy for estimating hepatic steatosis,¹³ and there are several methods for determining FF by MR imaging. Single-voxel MR spectroscopy (MRS) is usually used as the gold standard.^{14–16} However, MRS cannot give T_2^* -corrected FF values in the case of a fatty liver with iron deposition, whereas multi-echo gradient echo (MEGE) can correct T_2^* effects.¹⁷ In addition, single-voxel MRS uses a limited region of interest (ROI) to avoid contamination of portal veins and biliary ducts. In contrast, 3-point Dixon (DIXON) can scan the whole liver in one breath-hold and detect inhomogeneous fat accumulation but is also unable to correct the T_2^* effect.

We investigated the reproducibility, diagnostic accuracy, and sequence dependency of the FFs determined by the DIXON and MEGE methods compared to that by MRS.

Materials and Methods

Subjects

Our institutional review board approved the study design, and we obtained informed consent from all volunteers.

The study included 98 randomly recruited healthy volunteers (80 men, 18 women; aged 21 to 60 years; body mass index [BMI], 23.3 ± 3.1 [range, 17.3 to 33.7]). None of the volunteers had been checked for NASH, NAFLD, or iron deposition because they had no significant medical histories.

Scans and data processing

All volunteers underwent ^1H MR spectroscopy and MR imaging using a whole-body 1.5-tesla magnet (Achieva A-series, PHILIPS Medical Systems, Best, The Netherlands) equipped with a 16-channel XL-torso phased-array coil.

We first scanned the 3-plane T_2 -weighted image and DIXON and used those images to set the volume of interest (VOI) for the MRS scan we then performed, placing the VOI on the right hepatic lobe to avoid the portal vein, biliary structures, and inhomogeneous fat accumulation as much as possible. We then acquired an MEGE scan at the center of the location used for MRS.

To evaluate reproducibility, we randomly selected 10 volunteers (9 men, 1 woman; aged 29 to 53

years; BMI, 24.2 ± 1.8 [range, 22.3 to 27.6]) from the 98, to undergo repositioning and rescanning after the first scan. Two trained technologists (KI and SM, both with 3 years' experience) performed MRS and MR imaging. Figure 1 shows the representative fat and water images of DIXON, FF map of MEGE, and MRS spectra.

^1H MR spectroscopy

MRS was performed with a single-voxel, point-resolved spectroscopy sequence (PRESS) using parameters: repetition time (TR), 2000 ms; echo time (TE), 40 ms; voxel size, $30 \times 30 \times 30$ mm; 8 averages; 2048 points over 2500 Hz; and scan time of 18 ms on a single breath-hold. We performed iterative shimming of the VOI in the automatic mode. After scanning the liver using the automatic fitting software on the console, we measured the signal integrals of fats (CH_2 and CH_3 at 1.3 ppm) and water (H_2O at 4.7 ppm). Hepatic fat content was expressed as FF [$I_{\text{fat}}/(I_{\text{water}} + I_{\text{fat}}) \times 100$], where I_{fat} was the signal integral of fat and I_{water} was the signal integral of water.

Three-point DIXON

We performed DIXON with a 3-dimensional (3D) fast-field echo sequence and parameters: TR, 6.2 ms; $\text{TE}_1/\text{TE}_2/\text{TE}_3$, 1.6/3.2/4.8 ms; flip angle (FA), 10 degrees; matrix size, 128×95 ; field of view (FOV), 360×258 mm; pixel size, 2.8×2.7 mm; one average; slice thickness, 8 mm; scan range of global liver; and scan time, 18 ms on a single breath-hold. T_2^* was not corrected. Using the reconstructed fat and water image, one of the authors (KI) placed a region of interest (ROI) 30×30 mm at the location used for MRS, and the signal intensities of fat and water were measured. Hepatic fat content was expressed as FF [$S_{\text{fat}}/(S_{\text{water}} + S_{\text{fat}}) \times 100$], where S_{fat} was the signal intensity of fat and S_{water} was the signal intensity of water.

Multi-echo gradient echo

We performed MEGE using a 2D fast-field echo sequence and parameters: TR, 48 ms; TEs, 2.3/4.6/6.9/9.2 ms; 4 echoes; FA, 20 degrees; matrix size, 128×128 ; FOV, 360×360 mm; pixel size, 2.8×2.7 mm; one average; slice thickness, 10 mm; single slice; and scan time, 20 ms on a single breath-hold. To correct the T_2^* value, we obtained 4 echoes at serial opposed-phase and in-phase echo times (2.3, 4.6, 6.9, 9.2 ms). We used PRIDE research software (PHILIPS Medical Systems, Best, The Netherlands) to obtain the fat fraction image and T_2^* -corrected FF. First, we calculated the initial values of the T_2^* decay-corrected water

Fig. 1. A 34-year-old man. (A) Fat and (B) water image of DIXON; (C) fat fraction (FF) map of multi-echo gradient echo (MEGE); and (D) magnetic resonance (MR) spectra. FF value of DIXON was 13.1% in A and B. FF value of MEGE was 14.1% in C. FF value of MR spectroscopy (MRS) was 19.6% in D.

(S_{w0}) and fat-signal-intensity (S_{f0}) according to the following fitting model [1]:

$$S(TE) = \exp(-TE/T_2^*) \cdot ((S_{w0})^2 + (S_{f0})^2 + 2 \cdot S_{w0} \cdot S_{f0} \cdot \cos \Delta\omega \cdot TE)^{1/2}, \quad [1]$$

where TE is the echo time, T_2^* is the T_2^* value of tissue, and ω is the difference in resonance frequency of water and fat. In this model, the T_2^* of water and fat were compartmentalized, but it was too difficult to perform fitting.¹⁸ Therefore, the T_2^* decay terms of water and fat were conflated by fixing the phase differences of water and fat.¹⁹ We obtained a T_2^* -corrected FF image using S_{w0} and S_{f0} obtained by fitting. Hepatic fat content was expressed as FF [$S_{f0}/(S_{w0} + S_{f0}) \times 100$]. Using ImageJ software (available at <http://rsb.info.nih.gov/ij/>), one of the authors (KI) placed an ROI of 30×30 mm at the MRS location, and FF values were measured.

Data analysis

We summarized all continuous variables using means and standard deviations.

Reproducibility

Ten of the 98 volunteers were underwent scan-

ning twice with all 3 methods, and we analyzed each data set for sequence reproducibility.

Diagnostic accuracy

In 98 volunteers, we calculated performance statistics (sensitivity, specificity) for DIXON and MEGE methods using a threshold value that was 6.25% of the spectroscopic FF. This value was equivalent to an FF of 5.56% by wet weight, which previous studies identified as a classification threshold for fatty liver.^{14,20}

Sequence dependency

In 98 volunteers, we compared the FF obtained by DIXON and MEGE methods to that by MRS as the gold standard.

Statistical analysis

We evaluated the degree of agreement between the 2 repeated studies in terms of the mean absolute difference, 95% confidence intervals (CI) of the mean difference, and slope of the regression line. We used Pearson's correlation coefficient and Bland-Altman analysis to compare agreement among the repeated studies and the FF values by the 3 methods.²¹ We tested statistical significance

using Wilcoxon's t-test for repeated studies and paired t-test for sequence dependency, with statistical significance defined as $P < 0.05$.

Results

FF measurements of all 3 methods were fully implemented in all subjects. In 98 volunteers, the spectroscopic FF ranged from 0.0% to 32.5% (mean, 5.1%).

Reproducibility

Correlation coefficients that exceeded 0.93 ($P < 0.001$) in 10 volunteers for each repeated measurement demonstrated the high reproducibility of each FF (Fig. 2). The Bland-Altman plots showed mean differences between the repeated studies with regard to FF measurements as -1.27 (MRS), -0.16 (DIXON), and -0.06 (MEGE); 95% confidence intervals of the mean difference as $-3.40 \sim 0.82$ (MRS), $-1.85 \sim 1.35$ (DIXON), and $-1.05 \sim 0.65$ (MEGE); and slopes of the regression lines of 0.199

($P = 0.071$) (MRS), 0.171 ($P = 0.212$) (DIXON), and -0.054 ($P = 0.481$) (MEGE) (Fig. 3). Wilcoxon's t-test revealed no significant difference between repeated scans in MRS ($P = 0.193$), DIXON ($P = 0.922$), and MEGE ($P = 0.901$).

Diagnostic accuracy

Table shows performance statistics of DIXON and MEGE methods at the threshold value of 6.25% for spectroscopic FF. Sensitivity of DIXON was 82% and specificity, 96%; sensitivity of MEGE was 70% and specificity, 99%.

Sequence dependency

In 98 volunteers, the FFs determined by DIXON and MEGE correlated well with that by MRS ($r = 0.920$, $P < 0.001$) for each sequence (Fig. 4). The Bland-Altman plots showed that the mean differences between FFs determined by DIXON and MEGE, with regard to FF by MRS, were 0.93 and -1.16 , respectively. The 95% confidence intervals of the mean difference between FFs determined by

Fig. 2. Graphs showing reproducibility of fat fraction (FF) by magnetic resonance spectroscopy (MRS) (a), DIXON (b), and multi-echo gradient-echo (MEGE) (c) methods. The initial FF measurements are plotted against those of the repeated measurements. High reproducibilities of the FF were demonstrated, as reflected in correlation coefficients that exceeded 0.930 ($P < 0.001$) in 10 volunteers for each repeated measurement.

Fig. 3. Bland-Altman plots of the repeated studies by magnetic resonance spectroscopy (MRS) (a), DIXON (b), and multi-echo gradient-echo (MEGE) (c) methods. The mean differences between the repeated studies with each sequence were -1.27 , -0.16 and -0.06 , for MRS, DIXON and MEGE, respectively. The 95% confidence intervals of the mean difference were $-3.40 \sim 0.82$, $-1.85 \sim 1.35$, and $-1.05 \sim 0.65$; and the slopes of the regression lines were 0.199 ($P=0.071$), 0.171 ($P=0.212$), and -0.054 ($P=0.481$), for MRS, DIXON and MEGE, respectively.

Table. Diagnostic sensitivity and specificity of DIXON and multi-echo gradient-echo (MEGE) methods at a threshold value of 6.25% for spectroscopic fat fraction.

	DIXON	MEGE
Sensitivity	0.815 (22/27) [0.620, 0.935]	0.704 (19/27) [0.495, 0.870]
Specificity	0.958 (68/71) [0.880, 0.990]	0.986 (70/71) [0.935, 1.000]

Notes. We used numbers in parentheses to calculate sensitivities and specificities. Brackets enclose 95% confidence intervals.

DIXON and MRS were $0.80 \sim 2.30$ and those determined by MEGE and MRS were $-1.30 \sim 0.05$. The slopes of the regression lines as determined by DIXON and MEGE, with regard to MRS, were -0.655 ($P<0.001$) and -0.527 ($P<0.001$), respectively (Fig. 5). Paired t-test revealed that FFs determined by DIXON and MEGE were significantly different from that by MRS ($P<0.001$).

When FFs were less than 6.25% by MRS ($N=71$), only moderate correlation was observed be-

tween FFs by DIXON and MRS ($r=0.417$, $P<0.001$), and between FFs by MEGE and MRS ($r=0.493$, $P<0.001$). The Bland-Altman plots showed that the mean differences between FFs determined by DIXON and MEGE, with regard to FF by MRS, were 2.79 and 0.47, respectively. The 95% confidence intervals of the mean difference between FFs determined by DIXON and MRS were $2.40 \sim 3.10$ and those determined by MEGE and MRS were $0.10 \sim 0.75$. The slopes of the regression lines as determined by DIXON and MEGE, with regard to MRS, were -0.344 ($P=0.027$) and -0.343 ($P=0.017$), respectively. Paired t-test revealed that FFs by DIXON and MEGE were significantly different from FF by MRS ($P<0.001$).

When FFs exceeded 6.25% by MRS ($N=27$), strong correlation was observed between FFs by DIXON and MRS ($r=0.928$, $P<0.001$), and between FFs by MEGE and MRS ($r=0.936$, $P<0.001$). The Bland-Altman plots showed that the mean differences between FFs by DIXON and MEGE, with regard to MRS, were -3.52 and -5.05 , respectively. The 95% confidence intervals of the mean difference between FFs determined by

Fig. 4. Graphs showing sequence dependency of DIXON (a) and multi-echo gradient-echo (MEGE) (b) methods compared to magnetic resonance spectroscopy (MRS). Correlation coefficients of fat fractions (FFs) determined by DIXON and MEGE with the FF determined by MRS exceeded 0.920 ($P < 0.001$) in 98 volunteers for each sequence.

Fig. 5. Bland-Altman plots of fat fraction (FF) by DIXON (a) and multi-echo gradient-echo (MEGE) (b) methods compared to that by magnetic resonance spectroscopy (MRS). The Bland-Altman plots showed that the mean differences between FFs determined by DIXON and MEGE, with regard to FF by MRS, were 0.93 and -1.16 , respectively. The 95% confidence intervals of the mean difference between FFs determined by DIXON and MRS were $0.80 \sim 2.30$ and those determined by MEGE and MRS were $-1.30 \sim 0.05$. The slopes of the regression lines as determined by DIXON and MEGE, with regard to MRS, were -0.655 ($P < 0.001$) and -0.527 ($P < 0.001$), respectively.

DIXON and MRS were $-5.55 \sim -2.20$ and those determined by MEGE and MRS were $-6.85 \sim -3.80$. The slopes of the regression lines as determined by DIXON and MEGE, with regard to MRS, were -0.525 ($P < 0.001$) and -0.368 ($P = 0.006$), respectively. Paired t-test revealed that FFs determined by DIXON and MEGE were significantly different from that by MRS ($P < 0.001$).

Discussion

We investigated the sequence reproducibility of 3 methods and evaluated the diagnostic accuracy and sequence dependency of FFs determined by

DIXON and MEGE compared to those by MRS.

Each of the 3 MR methods showed high reproducibility. FFs determined by DIXON and MEGE systematically resulted in overestimation when fat content was less than 6.25%, probably because of relatively large background noise effects. When fat content was low, background noise increased the FF determined by DIXON.²² Similarly, fitting errors caused by background noise likely increased the FF determined by MEGE. However, FFs determined by both DIXON and MEGE resulted in improved diagnostic specificity (0.958 [DIXON]; 0.986 [MEGE]) at the 6.25% threshold. Therefore, FFs by DIXON and MEGE can be used for detect-

ing mild fatty liver.

In contrast, when the FF by MRS exceeded 6.25%, it was significantly higher than those by DIXON and MEGE, possibly because of MRS scan parameters (TR, 2000 ms; TE, 40 ms). At 1.5-tesla, the T_1 value of a normal liver is approximately 586 ms and the T_2 value, 40 ms, and the T_1 value of fat is approximately 343 ms and the T_2 value, 58 ms.²³ Because the signal intensity of water is more greatly affected than that of fat, non-corrected T_1 and T_2 values with MRS might tend to be overrated. This might cause the lower diagnostic sensitivity above the 6.25% threshold. However, there was high correlation of both the DIXON and MEGE methods with MRS when FF values exceeded 6.25%, which suggests the small impact of this factor on FF evaluation.

Our study was limited because we did not know if volunteers with mild fatty liver were affected by NASH and NAFLD. In the case of NASH or cirrhosis, measurement values with T_2^* non-corrected DIXON might not give correct values. Further investigation is needed that includes cases with known iron deposition. Nevertheless, DIXON can overcome the limitation of restricted ROI with single-voxel MRS, so it would be the most useful sequence to evaluate the distribution of fat accumulation in diffuse fatty liver disease. At this time, we recommend using DIXON first. In the case with iron deposition, a more accurate FF could be measured by adding an MEGE sequence for T_2^* correction.

Conclusion

We demonstrated high reproducibility of FF measurements using MRS, DIXON, and MEGE. Both DIXON and MEGE showed high specificities of more than 95%, with relatively low sensitivities, 82% (DIXON) and 70% (MEGE) compared to those by MRS. Compared to the FF determined by MRS, those by DIXON and MEGE showed sequence dependency because of proportional and additional errors with DIXON and a proportional error with MEGE.

References

1. Sanyal AJ. American Gastroenterological Association. AGA technical review on nonalcoholic fatty liver disease. *Gastroenterology* 2002; 123:1705–1725.
2. McCullough AJ. Update on nonalcoholic fatty liver disease. *J Clin Gastroenterol* 2002; 34:255–262.
3. Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA, Bacon BR. Nonalcoholic steatohepatitis: a proposal for grading and staging the histological lesions. *Am J Gastroenterol* 1999; 94:2467–2474.
4. Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology* 2005; 41:1313–1321.
5. Thampanitchawong P, Piratvisuth T. Liver biopsy: complications and risk factors. *World J Gastroenterol* 1999; 5:301–304.
6. Ratz V, Charlotte F, Heurtier A, et al. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. *Gastroenterology* 2005; 128:1898–1906.
7. Qayyum A, Chen DM, Breiman RS, et al. Evaluation of diffuse liver steatosis by ultrasound, computed tomography, and magnetic resonance imaging: which modality is best? *Clin Imaging* 2009; 33:110–115.
8. Zhong L, Chen JJ, Chen J, et al. Nonalcoholic fatty liver disease: quantitative assessment of liver fat content by computed tomography, magnetic resonance imaging and proton magnetic resonance spectroscopy. *J Dig Dis* 2009; 10:315–320.
9. Schwenzer NF, Springer F, Schraml C, Stefan N, Machann J, Schick F. Non-invasive assessment and quantification of liver steatosis by ultrasound, computed tomography and magnetic resonance. *J Hepatol* 2009; 51:433–445.
10. Mennesson N, Dumortier J, Hervieu V, et al. Liver steatosis quantification using magnetic resonance imaging: a prospective comparative study with liver biopsy. *J Comput Assist Tomogr* 2009; 33: 672–677.
11. Joseph AE, Savarymattu SH, al-Sam S, Cook MG, Maxwell JD. Comparison of liver histology with ultrasonography in assessing diffuse parenchymal liver disease. *Clin Radiol* 1991; 43:26–31.
12. Saadeh S, Younossi ZM, Remer EM, et al. The utility of radiological imaging in nonalcoholic fatty liver disease. *Gastroenterology* 2002; 123:745–750.
13. Joy D, Thava VR, Scott BB. Diagnosis of fatty liver disease: is biopsy necessary? *Eur J Gastroenterol Hepatol* 2003; 15:539–543.
14. Yokoo T, Bydder M, Hamilton G, et al. Non-alcoholic fatty liver disease: diagnostic and fat-grading accuracy of low-flip-angle multiecho gradient-recalled-echo MR imaging at 1.5T. *Radiology* 2009; 251:67–76.
15. Szczepaniak LS, Nurenberg P, Leonard D, et al. Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population. *Am J Physiol Endocrinol Metab* 2005; 288:E462–E468.
16. Kim H, Taksali SE, Dufour S, et al. Comparative MR study of hepatic fat quantification using single-voxel proton spectroscopy, two-point dixon

- and three-point IDEAL. *Magn Reson Med* 2008; 59:521–527.
17. Yu H, McKenzie CA, Shimakawa A, et al. Multiecho reconstruction for simultaneous water-fat decomposition and T_2^* estimation. *J Magn Reson Imaging* 2007; 26:1153–1161.
 18. Arai N, Miyati T, Matsunaga S, et al. [New method of determining regional fat fraction with modulus and real multiple gradient-echo (MRM-GRE)]. *Nippon Hoshasen Gijutsu Gakkai Zasshi* 2007; 63:312–318. [Article in Japanese]
 19. Parizel PM, Van Riet B, van Hasselt BA, et al. Influence of magnetic field strength on T_2^* decay and phase effects in gradient echo MRI of vertebral bone marrow. *J Comput Assist Tomogr* 1995; 19: 465–471.
 20. Longo R, Pollesello P, Ricci C, et al. Proton MR spectroscopy in quantitative *in vivo* determination of fat content in human liver steatosis. *J Magn Reson Imaging* 1995; 5:281–285.
 21. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; 1:307–310.
 22. Liu CY, McKenzie CA, Yu H, Brittain JH, Reeder SB. Fat quantification with IDEAL gradient echo imaging: correction of bias from $T(1)$ and noise. *Magn Reson Med* 2007; 58:354–364.
 23. de Bazelaire CM, Duhamel GD, Rofsky NM, Alsop DC. MR imaging relaxation times of abdominal and pelvic tissues measured *in vivo* at 3.0T: preliminary results. *Radiology* 2004; 230:652–659.
-