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Original Research Article

Role Of Diffusion Weighted Magnetic Resonance Imaging in Differentiation of benign from malignant liver lesions.

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Abstract:

Objective. Differentiation of benign from malignant liver lesions**. Methods:** The main sources of data for the study are patients from the following teaching Hospitals attached to Bapuji Education Association, J.J.M. Medical College, Davangere. 30 patients with focal liver lesions and additional 10 healthy volunteers with no focal liver lesion were studied to know to know normal ADC of liver

Result: Out of the total 85 focal liver lesions seen in 30 patients there were 63(74.1%) were malignant and 22(25.9%) were benign lesions. The number of malignant FLLs detected with DWI (62 out of 63 – 98.4%) was highly significant than that detected with T2 WI (P <0.001). However there was significant difference between the T2 weighted imaging and DWI for the detection of HCCs alone. This may be due most of HCCs were more than 2cm in size. However, there was no difference determined between T2 weighted imaging and DWI for the detection of benign hepatic lesions in our study. Mean ADC values obtained from normal liver parenchyma in benign and malignant group 1.25±0.04 x 10^{-3} mm^2/s. and 1.23±0.06 x 10^{-3} mm^2/s. respectively. Mean ADC of normal liver parenchyma (both benign and

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malignant group) was 1.24± 0.06 x 10^{-3} mm^2/s were not significant (ANOVA p=0.20).

Conclusion: Cysts and hemangiomas had the highest ADC values while malignant masses had the lowest. The lowest ADC values among the malignant masses belonged to metastases. Mean ADC values of malignant lesions were significantly lower than those of benign lesions: 0.92 x 10^{-3} mm^2/s V/s 2.68 x 10^{-3} mm^2/s respectively (*P*< .001). The Sensitivity of 98 %(61/62), Specificity of 100% with the ADC cutoff value 1.26 x 10^{-3} mm^2/s was obtained by normal distribution (mean ± 2SD) for differentiating between benign and malignant liver lesions.

Keywords: Benign, Malignant, Mean ADC values

INTRODUCTION: Hepatocellular carcinoma is the most common primary malignancy of the liver. Patients who are carriers of chronic hepatitis B or C virus infection, or those who have cirrhosis caused by alcohol or hemochromatosis are at greater risk of developing HCC.[1] The fibrolamellar variant of HCC, however, has usually no association with cirrhosis. HCC arises from dysplastic nodules.[2] Dysplastic nodules progress from low-grade dysplastic nodules to high-grade dysplastic nodules. High-grade dysplastic nodules may develop microscopic foci of HCC that then enlarge to become a frank malignant HCC. HCC can appear as a solitary or multifocal liver mass or as a diffuse infiltrative tumor. Portal-vein invasion and intrahepatic metastases and tumor capsule are characteristic features of HCC.[3]

Metastatic disease is the most common cause of malignant liver lesions, outnumbering primary hepatic neoplasm by 18 to 40 times.[4,5] Up to 75% of primary tumors drained by the portal venous system (pancreas, large bowel, small intestines and stomach) will have metastatic involvement at some stage of the disease. About 10% of these will have a solitary liver metastasis. This figure is much lower for other

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tumors such as those of the breast and thelung[1]. Metastases are classified as hypo- or hypervascular. The majority of liver metastases are hypovascular, usually originated from gastro-intestinal tract and from breast and lung carcinoma[6]. Hypovascular metastases are best depicted in portal-venous phase images. These metastases receive minimal blood supply from the hepatic artery. During the portal-venous phase, the liver parenchyma demonstrates marked enhancement while hypovascular metastases show only minimal enhancement, producing the greatest difference in liver-lesion signal intensity.[6,7] In arterial phase images, rim-enhancement has been reported to be highly specific for hypovascular metastases[8]. Hypervascular metastases are supplied by the hepatic artery and enhance rapidly after injection of gadolinium chelates. Typical hypervascular liver metastases arise from renal and breast carcinoma, islet cell tumors, melanoma, and sarcoma[6]. Thus, in arterial phase images, hypervascular metastases will show marked enhancement against a background of minimally enhancing liver parenchyma. In later phases the contrast agent within the tumour will washout tumour will become hypo – or iso to liver parenchyma.

Although, some metastases (e.g. from neuroendocrine tumours) appear to have the lowest ADC values among the hepatic malignant tumours, there is considerable overlap between pathological entities. Liver metastases that show a significant degree of central necrosis (e.g. colorectal liver metastases) frequently return higher mean ADC values than the normal liver[9] (Koh et al. 2006). Interestingly, Chan et al. reported that the mean ADC values for necrotic tumours were higher than those of hepatic abscesses[10] (Chan et al. 2001a, b). Sun et al. suggested that measuring the ADC value of a lesion compared with the liver may help to differentiate HCC from hepatic metastasis because HCC usually occurs in the setting of chronic hepatitis or cirrhosis while metastases often occur in the non-cirrhotic liver[11] (Sun et al. 2005).

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However, in clinical practice, it can be quite difficult to distinguish between metastases and other malignant hepatic tumours based on the signal intensity on high *b*-value DW-MR images or even with sophisticated calculations of the ADC value. It is thus important to interpret DW-MR images in conjunction with other MR imaging findings.

Material and Methods: The main sources of data for the study are patients from the following teaching Hospitals attached to Bapuji Education Association, J.J.M. Medical College, Davangere.

Sample size : 30 patients with focal liver lesions and additional 10 healthy volunteers with no focal liver lesion were studied to know to know normal ADC of liver.

Diagnosis on MRI was made with background of clinical context. Final diagnoses was reached in consensus with biopsy/FNAC, wherever applicable or clinical, laboratory, other imaging modality findings and follow up

Method of collection of data:

- All patients referred to the department of Radio diagnosis Patients of all age groups referred to MRI clinically suspected of focal liver lesions. Patients with indeterminate lesions detected on USG or CT in a period of 1 year 2 months from October 2011 to November 2012 were subjected for the study.

<u>Inclusion criteria</u> :

The study includes:

- All patients referred for MRI with clinically suspected focal liver lesions and patients with indeterminate liver lesions detected on USG or CT.

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- Incidentally detected focal liver lesions.

Exclusion criteria:

The study will exclude:

- All patients having cardiac pacemakers, prosthetic heart valves, cochlear implants or any metallic implants.
- Patient having history of claustrophobia.
- All patients who do not consent to be a part of the study.

Data Analysis:

Results expressed as mean, standard deviation, number and percentages. Categorical data was analyzed by chi-square test. p-value of 0.05 or less was considered for statistically significant. SPSS version 16 software used for data analysis.

Equipments:

The studies were conducted on the **PHILIPS ACHIEVA 1.5 TESLA MRI.** A 16 channel phased array XL-TORSO coil was used.

MRI PROTOCOL

T1WI, T2WI_TSE_FB, T2WI SPAIR in axial and coronal plane.

In- and out-of-phase T1-weighted GRE in axial plane.

Post Contrast Dynamic Study (Whenever Indicated): E-Thrive – 3D T1W TFE.

Respiratory-triggered (with a navigator-echo technique) Fat-suppressed(SPIR-selective presaturation using inversion recovery) single-shot echo-planar DW imaging

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was performed in the transverse plane with tridirectional diffusion gradients by using three *b* values (0, 500, and 1000 sec/mm^2) within the same acquisition, before contrast study.

The other parameters were as follows: repetition time msec/echo time msec, 2000–3000/67–82; matrix, 144 × 192; section thickness, 7 mm; intersection gap, 1.4 mm; field of view, 300–400 mm.

Acquisition time was 6-8mins (dependent on respiratory rate).

All ADCs were calculated on a workstation with standard software (Diffusion Calculation, Philips Medical Systems). The signal intensities for ADC calculation were measured by using operator-defined region-of-interest (ROI).

In large lesions the mean value of 3 different ROI measurements on the same slice was calculated

In lesions with necrotic or fibrous core, measurement of this area was avoided.

ADC of normal liver parenchyma was calculated in area away from focal liver lesions.

Results:

TABLE – 1: DETECTION RATE OF BENIGN AND MALIGNANT FLLS IN 30 PATIENTS (85 lesions) WITH DW AND T2 WEIGHTED IMAGING

Parameter	All lesions	Malignant	Benign
Total	85	63	22
T2WI	65 (76.51%)	44 (69.8%)	21 (95.5%)
DWI	82 (96.5%)	62 (98.4%)	20 (90.9%)

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Z-value	3.99	4.77	0.61
P-value	<0.001 HS	<0.001 HS	0.54 NS

The number of malignant FLLs detected with DWI (62 out of 63 – 98.4%) was highly significant than that detected with T2 WI (P <0.001).

There was no significant difference noted between DWI and T2 WI in detection of benign FLLs may be due to most of benign lesions were more than 2cm in size and benign lesions consisted only cystic and hemangioma lesion, and no solid benign lesions (FNH and adenoma) were studied.

TABLE – 2 : LESIONS DETECTION RATE STRATIFIED BY SIZE

Parameter	**<2 (n=34)**	**2.0 – 5 (n=31)**	**ε 5.0 (n=20)**
DWI	31 (91.2%)	31 (100%)	20 (100%)
T2 WI	14 (41.2%)	31 (100%)	20 (100%)
Z	5.13	0.0	0.0
P	<0.001 HS	1.00 NS	1.00 NS

The detection rate was stratified according to the lesion size. There was significant difference only for detection of FLLs with the diameter of less than 2 cm (p<0.001).

No significant difference between DWI and T2WI for FLLs more than >2 cm.

TABLE – 3 : INDIVIDUAL CASE DETECTION RATE OF FLLS IN 30 PATIENTS (85 lesions) WITH DW AND T2 WEIGHTED IMAGING

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Parameters	HCC	METS	CholangioCa	Hemangiomas	Simple cyst	Hydatid	Total
Total	23	36	4	6	9	7	85
T2WI	20 (87%)	22 (61%)	2 (50%)	6 (100%)	8 (86.9%)	7 (100%)	65 (76.5%)
DWI	23 (100%)	35 (97.2%)	4 (100%)	6 (100%)	7 (79.8%)	7 (100%)	82 (96.5%)
Z – value	1.85	4.21	2.00	0.00	0.64	0.00	3.99
P-value	0.064 NS	<0.001 HS	<.05 Significant	1.00 NS	0.52 NS	1.00 NS	<0.001 HS

In present study DWI was associated with significantly higher detection rate of metastatic (P<0.001)and cholangio carcinoma (P<.05) lesions when compared to T2WI. DWI MRI significantly improved the detection of metastases and cholangio carcinoma when compared to T2 WI. HCCs did not show significant detection rate, because most of HCCs were in more than >2cm in size. There was no significant difference in detection rate between DWI and T2W in FLLs more than 2 cm.

TABLE -4 : NUMBER OF FLLs MISSED ON DWI AND T2WI

Diagnosis	T2WI	DWI
HCC	3	0
METS	14	1
CholangioCa	2	0
Simple cyst	1	2
Hydatid cyst	0	0
Hemangioma	0	0
Total	**20**	**3**

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Total 20 lesions were missed by T2WI (HCC-3, metastasis-14, cholangio ca – 2 and simple cyst – 1), DWI missed 3 lesions (metastasis – 1, and simple cysts – 2).

TABLE – 5 : LESION CHRACTERIZATION ON DIFFUSION WEIGHTED IMAGING

Malignant lesions		**Diffusion**			**ADC**
		0	**500**	**1000**	
HCC (n=23)	Hyper	23 (100%)	23 (100%)	23(100%)	
	Hypo	-	-	-	23 (100%)
METS (n=36)	Hyper	35(97.22%)	20(97.22%)	20 (55.5%)	
	Hypo				20(97.22%)
	P-hyper		15 (41.6%)	15 (41.6%)	
	P.hypo				15 (41.6%)
	ND	1 (2.77%)	1 (2.77%)	1 (2.77%)	1 (2.77%)
CholangioCa (n=4)	Hyper	4 (100%)	4 (100%)	4 (100%)	
	Hypo				4 (100%)

Benign lesions	**Diffusion**			**ADC**
	0	**500**	**1000**	
Hemangioma (n=6)	Hyper 6 (100%)	Hyper – 5 (83.3%)	Mild hyper 5 (83.3%)	Iso – Hyper 5 (83.3%)
		Hyper with central hypo 1 (16.6%)	Iso – Hyper with central hypo 1 (16.6%)	H-hyper 1 (16.6%)
Simple cyst (n=9)	Hyper-7 (77.7%)	Iso – 6 (66.6%)	Iso – 6 (66.6%)	Hyper 7 (77.7%)
		Hypo – 1 (11.1%)	Hypo – 1 (11.1%)	
	ND-2 (22.2%)	ND-2 (22.2%)	ND 2 (22.2%)	ND – 2 (22.2%)
Hydatid (n=7)	Hyper – 7 (100%)	Moderate hyper 7	Iso–7 (100%)	IsoHyper 6 (83.3%)
		Iso – 0	Hyper - 0	H-Hyper – 1

Malignant lesions:

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All HCCs and cholangio ca. detected on DWI were hyperintense on DWI b=0, b=500, b=1000 and hypointense on ADC map.

Metastasis : All lesions were hyper on b=0. Most of the lesions were hyper (55.5%) and 41.6% were P.hyper on b=500 and b=1000. All these P.hyper lesions were more than 1 cm. Malignant lesions retained high signal intensity on high b values.

Benign lesions:

Hemangioma – DWI – on b=0 hyper and on high b=values (b=500 and b=1000) then was obvious signal intensity reduction. On ADC hemangiomas were Iso-hyper, or heterogeneously hyper. This may be due to T2 shine through effect.

Hydatid cysts - On low b-values (b=0) all lesions were hyper there was gradual decrease in signal on high b-values (b=500 moderate hyper and b=1000 – Iso). On ADC map all lesions were hyper.

Simple cysts: All detected lesions on DWI hyper on low b-values (b=0) and Iso – Hypo on high b-values (b=500, b=1000) on ADC all lesions were hyper intense.

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TABLE – 6 : MEAN ADC VALUE OF NORMAL LIVER PARENCHYMA

Normal liver parenchyma	No.of patients	Mean ADC ($x10^{-3}$ mm^2/s) Mean±SD
Benign group	11	1.25±0.04
Malignant group	19	1.23±0.06
No FLL group	10	1.26±0.02

ANOVA, F=1.66, p=0.20, NS

There was no significant difference of mean ADC value of liver parenchyma between all three groups. Mean ADC value of normal liver parenchyma is 1.24 ± 0.06 x 10^{-3} mm^2/s.

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TABLE – 7 : MEAN ADC FOR EACH TYPE OF FLL

Diagnosis	No.of lesions (n=82)*	ADC (x 10^{-3} mm^2/s)	
		Mean	SD
HCC	23	1.03	0.10
Mets	35	0.8	0.11
CholangioCa	4	1.21	0.11
Hemangioma	6	2.04	0.31
Simple hepatic cyst	7	3.1	0.08
Hydatid cyst	7	2.79	0.11

* in 3 lesions no ADC detected.

Simple cysts had high ADC value, and malignant had lowest value. Among malignant, metastases had lowest ADC ($0.8\pm0.11 \times 10^{-3} mm^2/s$)

Box plots of the ADC values of 82 FLLs (3 lesions were not detected on DWI).Boxes stretch across interquartile range (IR); median is shown as line across each bar; ADC values of metastases overlapped with ADC values of hepatocellular carcinomas (HCC).

In the present study the mean ADC values of malignant lesions were significantly lower than those of benign lesions (0.92×10^{-3} mm^2/s V/s 2.68×10^{-3} mm^2/s) ($p<0.001$).

Box plot of ADC values calculated for 62 malignant lesions and 20 benign. With the optimal cutoff ADC value of 1.50×10^{-3} mm^2/s to differentiate benign from malignant liver lesions.

TABLE – 8 : DIAGNOSTIC VALIDITY OF ADC IN DIFFERENTIATING MALIGNANT V/S BENIGN ADC CUTOFF = $1.26x10^{-3}mm^2/s$ (normal distribution) (mean ± 2SD)

ADC x $10^{-3}mm^2/s$	Malignant	Benign	Total

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<1.26	61	0	61
ε 1.26	1	20	21
Total	**62**	**20**	**82**

Sensitivity	61/62	=	98%
Specificity	20/20	=	100%
PPV	61/61	=	100%
NPV	20/21	=	95%
Overall accuracy	81/82	=	99%

TABLE – 9 : DIAGNOSTIC VALIDITY OF ADC IN DIFFERENTIATING MALIGNANT V/S BENIGN WITH ADC CUTOFF =1.5 x$10^{-3}$$mm^2$/s

ADC x $10^{-3}$$mm^2$/s	**Malignant**	**Benign**	**Total**
<1.50	62	0	62
ε 1.50	0	20	20
Total	**62**	**20**	**82**

Sensitivity	62/62	=	100%
Specificity	20/20	=	100%
PPV	62/62	=	100%
NPV	20/20	=	100%
Overall accuracy	82/82	=	100%

In the present study the difference between mean ADC values of simple cyst and hydatid cyst was significant.

In the present study the difference between mean ADC values of cholangio carcinoma and metastasis was significant

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In the present study the difference between mean ADC values of HCC and metastasis was significant.

Even with significant difference, there was lot of overlap of ADC values among HCCs and metastasis.

Discussion: All HCCs and cholangio carcinoma were hyperintense on DWI trace images(b=0, b=500 and b=1000) and hypointense on ADC map. All HCCs and cholangio carcinoma lesions retained high signal intensity on high b values.

All metastasis detected on DWI were hyperintense on b=0 and on high b values (b=500 and b=1000) most of lesions where hyper (55.5%) and others (41.6%) showed peripheral rim hyperintensity, one (2.77%) lesion was not detected on DWI.

All metastatic lesions which showed peripheral rim hyperintensities on high b values where more than 1 cm in size.

These findings were similar to Scurr ED et al[12], who found that colorectal liver metastases showed rim high signal intensity, uniform high signal intensity or variegate high signal intensity at b value of 500 s/mm^2 on DW-MRI. For metastases δ 1 cm in diameter, we found that the uniform pattern was most common, which may be difficult to distinguish from other solid liver lesions. However, for lesions >1 cm in diameter, the rim pattern was the most common

Benign lesions:

Hemangioma: DWI – on low b values (b=0) hyper and on high b=values (b=500 and b=1000) there was obvious signal intensity reduction. Necrotic parts were hypointense on high b values.

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Haemangiomas display high signal intensity on low b-values DW-MR images, but usually retain some of their high signal intensity at high b-value (b = 1,000 s/mm^2) DW-MRI. This may be due to T2 shine through effect.[13,14]

Simple cysts: All detected lesions on DWI hyper on low b-values (b=0) and iso – hypo on high b-values (b=500, b=1000). On ADC all lesions were hyperintense.

Hydatid cysts: On low b-values (b=0) all lesions were hyper and there was gradual decrease in signal on high b-values (b=500-mild hyper and b=1000 – Iso). On ADC all lesions were hyper.

These findings where different from Inan N et al[15] On trace DWI (b = 1,000 s/mm^2), most hydatid cysts were hyperintense, whereas most simple cysts (40/43, 93%) were isointense with the liver.[15]

In our study all hydatid cyst were moderate hyperintense on b=500 and isointense on b=1000 DWI images.

On low b-value diffusion- weighted MR images, all masses were observed as hyperintense, whereas on high b-value images signals of cysts disappeared and signals of hemangiomas obviously decreased. In contrast, since there is a limitation of diffusion in solid tumors, they were also observed as hyperintense on high b-value diffusion weighted image and these results similar to those obtained by several others.[13,14]

EVALUATION OF NORMAL LIVER PARENCHYMA

Mean ADC values obtained from normal liver parenchyma in benign and malignant group 1.25±0.04 x 10^{-3} mm^2/s and 1.23±0.06 x 10^{-3} mm^2/s. respectively. Mean ADC values obtained from normal liver parenchyma in group with no FLL (healthy volunteers) 1.26± 0.01 x 10^{-3} mm^2/s. where not significantly different (ANOVA, F=1.66, P=0.20 NS).

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Overall mean ADC of normal liver parenchyma in all 3 groups was 1.24± 0.05 x 10^{-3} mm^2/s. These findings were similar to Gourtsoyianni S et al[16]

ADC values were obtained for all 82 lesions detected by DWI.(3 lesions were not detected on DWI).

The mean ADC value of the focal liver lesions in our study were as follows: simple cysts (3.11+/- 0.08 x 10^{-3} mm^2/s), hydatid cysts (2.79 +/- 0.11 x 10^{-3} mm^2/s), hemangiomas (2.04+/- 0.31 x 10^{-3} mm^2/s), cholangiocelluar Carcinoma(CCC) (1.21+/-0.11x10^{-3} mm2/s) hepatocellular carcinomas (HCC) (1.03+/- 0.10 x 10^{-3} mm^2/s), metastases (0.81 +/- 0.11 x 10^{-3} mm^2/s).

Cysts and hemangiomas had the highest ADC values while malignant masses had the lowest. The lowest ADC values among the malignant masses belonged to metastases.

Mean ADC values of malignant lesions were significantly lower than those of benign lesions: 0.92 x 10^{-3} mm^2/s V/s 2.68 x 10^{-3} mm^2/s respectively (P< .001).

The ADC cutoff value 1.26x 10-3 mm2/s was obtained by normal distribution (mean ± 2SD).

With 1.26x$10^{-3}$$mm^2/s$ cutoff the Sensitivity of 98% (61/62), Specificity of 100% (20/20), PPV of 100% (61/61), NPV of 95% (20/21), Overall accuracy of 99 %(81/82) was obtained.

According to general observation and analysis of all ADC value of all FLLs, ADC measurements were capable of differentiating between benign and malignant liver lesions with a diagnostic accuracy of 1.0, sensitivity and specificity of 100% using a cutoff ADC value of 1.50×10^{-3} mm^2/s.

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Mean ADC value in differentiating between HCC and Metastasis was highly significant ($p<0.001$).

Despite significant differences in mean ADC of HCC and Metastasis FLLs on a group basis, characterization of FLLs by using ADCs showed overlap.

In the present study the difference between mean ADC values of simple cyst and hydatid cyst were significant. (3.11 ± 0.08 V/s $2.79 \pm 0.12 \times 10^{-3}$ mm^2/s) These findings were comparable to Inan N. et al.[15]

Benign hepatic lesions have generally higher ADC values compared with malignant lesions, with variable degree of overlap[13,]. Different ADC cutoffs ($1.4–1.6 \times 10^{-3}$ mm^2/sec) have been described in the literature, with a reported sensitivity of 74%–100% and specificity of 77%–100% for diagnosing malignant lesions. The ADCs of various benign and malignant hepatic lesions from selected published studies are summarized in table-30 given below.

Conclusion: Cysts and hemangiomas had the highest ADC values while malignant masses had the lowest. The lowest ADC values among the malignant masses belonged to metastases. Mean ADC values of malignant lesions were significantly lower than those of benign lesions: 0.92×10^{-3} mm^2/s V/s 2.68×10^{-3} mm^2/s respectively ($P< .001$). The Sensitivity of 98 %(61/62), Specificity of 100% with the ADC cutoff value 1.26×10^{-3} mm^2/s was obtained by normal distribution (mean ± 2SD) for differentiating between benign and malignant liver lesions

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