

ORIGINAL RESEARCH

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Diffusion weighted magnetic resonance imaging in differentiation of small focal liver lesions (≤ 10 mm) detected in patients with extrahepatic primary malignancy**Ahmet Soyucok¹, Kerim Aslan², Murat Danaci², Ilkay Camlidag²**¹*Denizli State Hospital, Department of Radiology, Denizli, Turkey*²*Ondokuz Mayıs University Faculty of Medicine, Department of Radiology, Samsun, Turkey*

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Abstract

The purpose of the study is to assess the advantages of diffusion weighted resonance imaging (DWI) prospectively in the metastasis and benign differentiation of small (≤ 10 mm) focal liver lesions (FLL) detected in routine ultrasonography and/or computed tomography screening of patients with extrahepatic primary malignancy. A total of 77 small FLLs (33 metastasis, 27 cyst, 17 hemangioma) of 53 patients who received DWI in addition to conventional magnetic resonance imaging were assessed by 2 independent readers prospectively. Apparent diffusion coefficient (ADC) values were measured for each FLL. T-test was used to assess the statistically significant difference between average ADC values in differentiating between metastasis and benign FLLs. In the metastasis and benign differentiation of small FLLs, optimum cutoff values of ADC values were found by using receiver operating characteristic (ROC) analysis. Average ADC values of small focal liver metastases were statistically significantly lower than those of benign FLL ($p < 0.001$). Small focal liver metastases were differentiated from benign FLL with 100% sensitivity and 97.1% specificity by using 1.44×10^{-3} s/mm² cutoff ADC value. This study shows that DWI can be useful in differentiating whether incidentally found small FLL is metastasis in patients who have extrahepatic primary malignancy.

Keywords: Diffusion-weighted imaging, apparent diffusion coefficient, small focal liver lesions**Introduction**

Although the recent developments in liver imaging modalities enable the detection of small lesions in the liver, there are still difficulties in the characterization of lesions. These small (≤ 10 mm) focal liver lesions (FLL) appear in patients who have incidental or known primary cancer. In patients with extrahepatic primary malignancy, liver is the organ which is frequently found to have metastasis. A number of studies have shown 12.7–50% of cancer patients to have small FLL and although a great number of these are benign, 5–27.5% of the lesions have been shown to be malign [1, 2]. In patients with extrahepatic primary malignancy, deciding on whether lesions smaller than 10 mm. are metastasis is very important in terms of the patient's prognosis and the correct planning of the treatment. Histopathological diagnosis of small

FLL with biopsy is frequently technically difficult. For this reason, an imaging technique which characterizes small FLL with high sensitivity and specificity is required.

The use of magnetic resonance imaging (MRI) is becoming widespread in liver imaging due to its many advantages such as high contrast resolution, absence of ionizing radiation. In general, lesion morphology, signal intensity and contrast enhancement pattern are assessed during FLL characterization with MRI. Diagnostic accuracy rates have been reported to increase with the quantitative measurement of T2 relaxation times of FLL [3]. In addition, using liver-specific contrast agents increases the diagnostic accuracy of liver lesions [4]. Despite all these MRI applications, there is still overlapping between benign and malign FLL.

Diffusion weighted imaging (DWI) has a wide potential of use in liver due to providing additional qualitative and quantitative information to conventional MRI sequences and being a fast and non-contrast technique. It is especially useful in patients who have risky severe renal dysfunction for nephrogenic systemic

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fibrosis [5]. DWI examines random microscopic motions of water molecules in the tissue and in this method; imaging contrast depends on the molecular motion of water. As a result, it provides quantitative and qualitative information which reflect the changes in cellular level. By using DWI, apparent diffusion coefficient (ADC), which allows quantitative measurement in proportion with the motions of direct water molecules, can be calculated [6, 7]. DWI is useful in the detection, characterization [8-10] and treatment response of FLL [5,11]. Small FLL studies conducted with DWI included small hepatocellular carcinoma and small intrahepatic cholangiocarcinoma in general [12-19]. These studies reported that DWI can be useful in the detection and characterization of lesions. A small number of studies have used DWI in the characterization of small FLLs including metastasis. These studies have shown that DWI can help in lesion characterization [20-22]. All of these studies are retrospective and to the best of our knowledge, we have not come across any prospective studies in literature that have used DWI in the characterization of small FLL in patients with extrahepatic primary malignancy.

The purpose of this study is to assess the advantages of DWI prospectively in the metastasis and benign differentiation of small (≤ 10 mm) FLL detected in routine ultrasonography and/or computed tomography screening of patients with extrahepatic primary malignancy.

Material and Methods

Patients

The local ethics committee approved the study and a signed written informed consent was obtained from each patient. 111 small FLLs (n=111) of 78 patients diagnosed with extrahepatic primary malignancy who were 18 and older, who could cooperate and who were detected to have small focal lesion (≤ 10 mm) in the liver with routine ultrasound and/or CT screening were included in the study. 3 patients (n=4) with general MR contraindications such as claustrophobia and implanted pacemakers or coils; 4 patients (n=6) who had received chemotherapy or radiotherapy within the last three months before MR screening; 9 patients (n=13) whose DWIs were not sufficient enough to assess due to severe motion artefacts and 7 patients (n=10) who did not have definitive diagnosis with biopsy for sufficient follow up were excluded from the study. Finally, 53 patients (n= 77) (29 male, 24 female; age range, 36–81 years; mean age [$\pm$ SD], 58.2 ± 13.8 years) were included in the study. In patients who had more than three lesions (n=3), maximum three lesions were chosen randomly for ADC measurement.

Extrahepatic primary malignancies in 53 patients were as follows: pancreas adenocarcinoma (n=3), stomach adenocarcinoma (n=2), colorectal adenocarcinoma (n=13), renal cell carcinoma (n=6), endometrioid adenocarcinoma (n=3), cervix adenocarcinoma (n=2), breast cancer (n=7), malign melanoma (n=1), ovary carcinoma (n=2), surrenal cancer (n=1), liposarcoma (n=1), bladder cancer (n=2), Hodgkin lenfoma (n=2) and lung cancer (n=8). The lesions were detected by using settled imaging criteria [23, 24] with stable appearance and size in images followed in simultaneous cases with a follow-up period of at least six months. 33 metastatic lesions of 20 patients were lesions diagnosed with growth in follow-up imaging including CT and/or MRI. Follow-up time was between 6 and 15 months with an average of 8.4 months.

Lesion diameters were between 5-10 mm, with an average of 8.2 mm. 27 simple liver cysts of 18 patients were diagnosed with typical US findings and absence of solid component contrasted when precontrast and postcontrast images were compared with CT and/or MRI and not showing difference in follow-up with US (Follow-up time between 6-12 months, with an average of 9.2 months). Lesion diameters were between 6-10 mm, with an average of 8.4 mm. 17 hemangioma in 15 patients were diagnosed with obvious hyperintense in well-demarcated T2-weighted images, with peripheral nodular contrast in arterial phase in CT and/or MRI and increase in contrast to the central in the late phase and with no change in follow-up with CT or MRI (Follow-up time between 7-12 months, with an average of 9.8 months). Lesion diameters were between 6-10 mm, with an average of 8.2 mm.

MR Imaging

All MR images were obtained by using 1.5-T superconducting MR unit with phased-array multicoids (Siemens Magnetom Symphony Quantum, Erlangen, Germany). MR images were obtained in all patients according to established routine MR imaging protocol in our institution. Routine examination sequences: true fast imaging with steady-state free precession (TrueFISP) coronal [repetition time/time to echo (TR/TE): 4.3 ms/15.2 ms, slice thickness: 6 mm, field of view (FOV): 400 mm, matrix 230 x 256, flip angle: 78, number of signal averages (NEX): 1], T2- weighted HASTE fat-suppressed axial gated (TR/TE: 1000 ms/83 ms, slice thickness: 5 mm, FOV: 450 mm, matrix 144 x 256, flip angle: 150, NEX: 2), T1- weighted spoiled gradient-recalled-echo axial [TR ms/TE ms, 172/5.24 (in-phase), 2.38 (out-of-phase), slice thickness: 5 mm, FOV: 500 mm, matrix 116 x 256, flip angle: 70, NEX: 1], three-phase dynamic axial contrast-enhanced fat-suppressed 3D spoiled gradient echo (TR/TE: 5.11 ms/ 2.37 ms, slice thickness: 2.5 mm, FOV: 500 mm, matrix, 116 x 256, flip angle: 15, NEX: 1).

DWI was applied before contrasted sections were taken. DWI sequences were obtained from SE-SSEPI by using free-breathing, parallel imaging and finger pulse trigger in the axial plane. b values were 0, 800 sn/mm^2 . Technical parameters were as follows; TR / TE: 4600 ms / 95ms, section thickness: 5 mm, FOV: 480 mm, matrix 104 x 128, bandwidth: 1346 Hz / Pixel, NEX: 6, distance factor % 30, EPI factor: 104, trigger pulse: 1, parallel acquisition techniques (PAT) factor, 2; PAT mode was parallel imaging modified sensitivity encoding (mSENSE).

Imaging Analysis

All of the images involving DWI for ADC measurements were transferred to a separate Workstation (Leonardo console, software version 2.0; Siemens). b value of 1000 s/mm^2 were used as the strength of motion-probing gradient pulse along the x, y, and z axes, making trace DW images on which all data produced in each direction of the motion-probing gradient pulse were synthesized. The ADC maps were created automatically by the system from the trace-weighted images with b value of 1000. The mean ADC values of all the lesions for b values of 1000 were measured on these maps. Two radiologists were blinded to the diagnosis of the lesions and to the results of the other MR imaging sequences, and of the patients' other clinical information. They performed the measurements independently. In ADC maps, ADC measurements were made through hand-drawn circular region of interest (ROI) with a diameter between 5-8 mm placed on the maps for each small FLL.

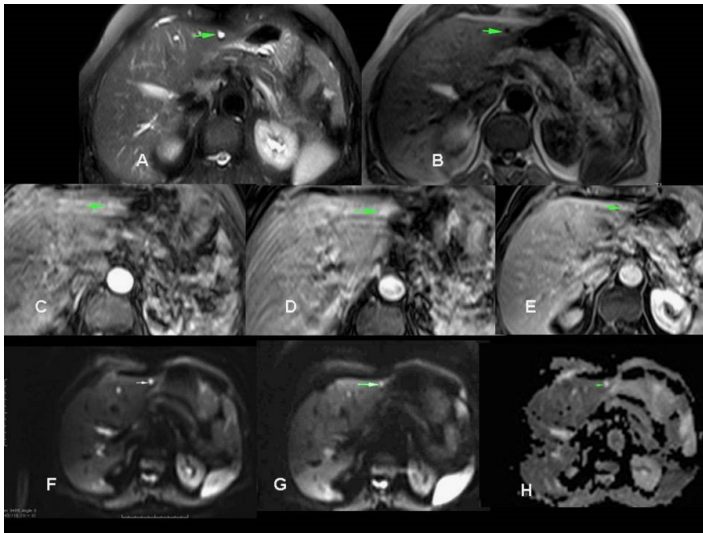


Figure 1. Hemangioma in a 65-year-old male patient with colorectal cancer. Lesions which are well-defined, hyperintense on T2-weighted series (A), hypointense on T1-weighted series (B) relative to liver parenchyma, homogeneous intense enhancing in arterial (C) and portal venous phase (D), isointense with the liver in the late phase (E) on liver segment II. Lesion is slightly hyperintense on DWI (F, G) in relation to parenchyma, hyperintense on ADC map obtained by DWI (H), and not showing diffusion restriction

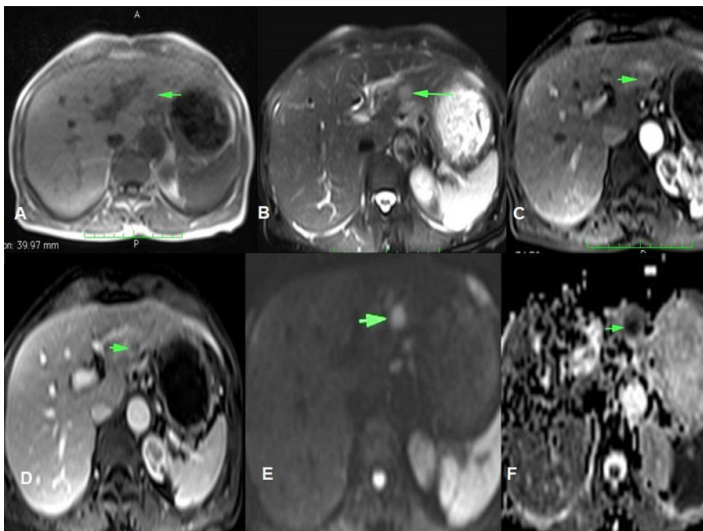


Figure 2. Breast cancer metastasis in a 65-year-old female. Lesions which are well-defined, hyperintense on T2-weighted series (A), hypointense on T1-weighted series (B) relative to liver parenchyma, peripheral enhancement in arterial (C) and portal venous phase (D), on liver segment III. Lesion is hyperintense on DWI (E) in relation to parenchyma, hypointense on ADC map obtained by DWI (F), and showing diffusion restriction

Statistical Analysis

All statistical analyses were conducted by using SPSS (Statistical Package for Social Sciences, version 16.0, SPSS Inc., Chicago, IL, USA). Average ADC values were calculated separately for metastasis, cyst, hemangioma and FNH. ADC values were presented as arithmetic mean $\pm$ standard deviation. In addition, average ADC values of metastases and average ADC values of all benign lesions were calculated. T-test was used to assess the statistically significant difference between ADC values in the differentiation of metastases from benign lesions and the differentiation between sub-groups (metastasis – cyst and metastasis – hemangioma). In the differentiation of metastasis and benign lesions, optimum cutoff values of ADC were found by using receiver operating characteristic (ROC) analysis. In addition, ROC analysis was used

to measure sensitivity, specificity and area under the curve (AUC) according to cutoff ADC value to find out the optimal cutoff ADC value that can be used in the differentiation between between sub-groups (metastasis – cyst and metastasis – hemangioma) and to differentiate between all groups. Interobserver agreement between the 2 readers was assessed using weighted Cohen kappa (κ) statistics. A κ value of 0.4 or lower indicated poor agreement, 0.41–0.60 indicated moderate agreement, 0.61–0.80 indicated good agreement, and 0.81–1.0 indicated excellent agreement. As some patients had more than one liver mass, the cluster effect was considered in ROC curve analysis. A P value less than 0.05 was considered to indicate a statistically significant difference.

Results

Table 1 shows number of lesions, mean $\pm$ SD ADC values for metastasis, cyst, hemangioma, FNH and benign FLL.

Table 1. Mean ADC values for metastasis, cyst, hemangioma, focal nodular hyperplasia and all benign lesions*

	Lesion number	ADC (Mean $\pm$ SD)	K values
Metastasis	33	1.14 $\pm$ 0.91	0.876
Hemangiomas	17	2.10 $\pm$ 0.43	0.926
Cysts	27	2.75 $\pm$ 0.56	0.843
All Benign lesions*	45	2.52 $\pm$ 0.72	

*Except for the K values, apparent diffusion coefficient (ADC), *hemangiomas and cysts,

In the whole FLL, the highest ADC values were found in cysts (2.75 $\pm$ 0.7 sn/mm²), while the lowest ADC values were found in metastases (1.14 $\pm$ 0.6 sn/mm²). ADC values of cysts and hemangiomas were found to overlap, while less overlapping was found between ADC values of hemangiomas and metastases. No overlapping was found between ADC values of cysts and metastases. Average ADC values of metastases were found to be statistically lower than those of benign FLL (P<0.001), cysts (P<0.001) and hemangiomas (P<0.001). The agreement for metastasis, hemangiomas and cyst ADC measurements was excellent between the two radiologists (κ values = 0.876, 0.926, and 0.843, respectively).

Table 2 shows cutoff, sensitivity, specificity, and AUC values for ADC in differentiating metastases from benign FLL, from hemangiomas and from cysts with ROC analysis.

Table 2. Cutoff, sensitivity, specificity, and AUC values for ADC in differentiating metastases from all benign lesionsa, from hemangiomas and from cysts with ROC analysis*

	AUC	Cutoff	Sensitivity	Specificity
Metastasis-All Benign lesionsa	0.98	1.44	% 100	% 97.1
Metastasis -Cysts	1.00	1.64	% 100	% 100
Metastasis- Hemangiomas	0.96	1.43	% 100	% 92.3

*Except for the K values, apparent diffusion coefficients (ADC), area under the curve (AUC). ahemangiomas and cysts

Discussion

This study allowed for the characterization of small ($\leq$ 10 mm diameter) FLL as benign or metastasis with high accuracy by

using DWI in patients with extrahepatic primary malignancy and agreement was perfect between observers.

In patients with extrahepatic primary malignancy, classification of FLL as benign or metastasis is important for optimal treatment plan. Although most of the FLLs smaller than 1 cm which are detected incidentally are benign, 5–27.5% are malign [1,2]. It is not only invasive, but also technically difficult to obtain the tissue diagnosis of these lesions. For this reason, small FLLs should be diagnosed with non-invasive techniques [25]. Small FLL visibility has increased with multidetector computed tomography (MDCT). However, since attenuation measurement of small FLL is not reliable due to pseudo contrast enhancement and partial volume effect, malign-benign differentiation is not possible and assessed as indecisive lesion. It has been found that sometimes these lesions have lower density values than 20 Hounsfield Unit even in contrast enhancement examinations and this makes it difficult to define the cystic metastases especially in the liver [25]. It has been found that a great number of small FLL lesions (≤ 10 mm) do not show a specific contrast enhancement pattern unsuitable for typology in dynamic contrast examinations or do not involve contrast. In addition, some hemangiomas and metastases can be insufficient in CT or MRI characterization due to atypical contrast involvement [25]. With MRI, small cystic lesions can be differentiated since they do not show T2 hyperintensity or contrast. However, non-cyst small FLL which does not show specific contrast can present a problem. In the characterization of lesions smaller than 10 mm by using conventional T1, T2 weighted and dynamic contrasted sequences, sensitivity and specificity have been reported as 66.7%-83.3% and 86.7%-95.5%, respectively [26,27].

ADC formed from DWI measures the total magnitude of water diffusion in tissue independently of direction and gives information about the tissue cellularity and nucleus-to-cytoplasm ratio [28]. DWI has a wide area of use in the detection, characterization of FLL and in the assessment of tumour's response to treatment [5, 8-11]. DWI is an imaging method which does not require contrast agent and which can be applied fast. This way, it can be added to existing imaging protocols without a significant increase in the application time [5].

There are studies which show that DWI is superior to T2W [29,30] and super paramagnetic iron oxide (SPIO) contrasted MR [31] imaging in the detection of small FLL. In their study, Coenegrachts et al. [31] reported that SPIO contrasted imaging and DWI combination allowed for FLL characterization. In their study, they reported that if a lesion can be seen in post-contrast images, these images can provide additional information about the nature of the lesion. However, the size of the lesions was generally > 10 mm in their study.

Small FLL characterization with DWI generally included small hepatocellular carcinomas and small intrahepatic cholangiocarcinomas [12-19]. These studies reported that DWIs were complement and even superior to dynamic MRI in the diagnosis of small hepatocellular carcinomas [12-15,17]. Park et al. [19] reported that DWI was a reliable method in differentiating small intrahepatic mass-forming cholangiocarcinomas from small hepatocellular carcinomas. None of these studies researched the characterization of small metastases in liver.

In their study they conducted with DWI for small FLL (≤ 10 mm) characterization including metastases, Holzapfel et al. [20] showed that when ADC cutoff value was taken as 1.41×10^{-3} sn/mm², malignant lesions could be differentiated from benign lesions with 90.8% sensitivity and 89.9% specificity. They reported that even when the diameters of DWI lesions were 10 mm or less, they could help in characterizing FLL. In their recent study, Jeon et al. [21] showed that in pancreatic cancer that can be potentially resected, adding DWI to MRI can provide better diagnostic performance in FLL characterization. However, none of these studies were prospective. Our study prospectively assessed the uses of DWI in the differentiation of metastasis and benign in small (≤ 10 mm) FLL in patients with extrahepatic primary malignancy. In the current study, average ADC values of metastases were reported to be significantly lower than the ADC values of benign FLL ($P < 0.001$), cysts ($P < 0.001$) and hemangioma ($P < 0.001$). Our study differentiated small focal liver metastases from benign FLL with a sensitivity of 100%, a specificity of 97.1% and 0.98 AUC by using 1.44×10^{-3} sn/mm² cutoff ADC value. In addition, in the current study, cutoff ADC, sensitivity, specificity and AUC values in differentiating metastases from hemangiomas and from cyst were 1.43, 100%, 92.3% and 0.96; and 1.64, 100%, 100% and 1, respectively. In the current study, decreased ADC values in metastasis can show increased cellularity and high nucleus-to-cytoplasm ratio. In their study, Holzapfel et al. [20] reported that although metastases showed significantly low ADC values when compared with cysts and hemangioma, there was significant overlap between metastases and solid benign FLL (FNHs, adenomas) and between metastases and hemangioma. Similarly, there were values in our study which showed overlap between ADC values of hemangioma and metastases.

Our study had a few limitations. Firstly, the most important limitation of this study is the small number of solid benign FLL. In order to confirm the results of our study, studies which include a great number of solid benign FLLs are needed. Secondly, as in many studies on small FLL, histopathological confirmation could not be made. However, the fact that all MR sequences and sectional follow-up imaging was assessed by two readers caused a low probability of misclassifying the lesions. Benign lesions were diagnosed with typical MRI, CT and US characteristics, contrast patterns and not showing growth in follow-up [23]. Metastases were lesions which appeared during imaging including CT and MRI and they were diagnosed with growth [24]. Thirdly, 77.9% (60/77) of the FLL analyzed in this study were metastases or cysts, that is, FLL with very low or very high ADC values. With higher number of FLLs which have intermediate ADC values (for example hemangiomas, solid benign FLL) DWI accuracy can be worse in the characterization of FLL. Because, in case of lesions such as hemangiomas and solid benign FLL having ADC values close to the ADC values of malignant lesions, the possibility of overlapping between malignant-benign ADC values increases. For this reason, DWI can seem to have decreased ability in lesion characterization. Especially very high ADC values in cysts can incorrectly increase the ability of DWI in differentiating between benign and malignant lesions. Because, since cyst has high ADC values, in case of too many cysts, the possibility of overlapping with ADC values of malignant lesions decreases. However, since metastases and cysts were the most commonly seen FLL in oncologic patients, we did not exclude patients with

cyst in our study. Fourthly, the most important limitation to the use of ADC values is that the mono-exponential calculation is heavily influenced by the b value. Therefore, Dijkstra et al. [32] emphasized that liver measurements should be undertaken using bi-exponential models to avoid microperfusion contamination. Therefore, quantitative ADC measurements are not used in routine practice for the characterization of liver lesions. Finally, in our study, FLL with an average diameter of 6.9 mm was analyzed by using 5 mm section thickness. For this reason, partial volume effects probably influenced the results to a certain extent.

Conclusion

Especially in patients with a diagnosis of primary cancer, classifying small FLL as benign or metastasis is very important for optimal treatment plan. This study differentiated small focal liver metastases from benign FLL with a diagnostic accuracy of 98% by using 1.44×10^{-3} sn/mm² cutoff ADC. Our study showed that DWI can be useful in differentiating whether incidentally detected small FLL is a metastasis in patients with extrahepatic primary malignancy. A great number of studies including solid benign FLL (FNHs, adenomas) will be required to confirm our results in the future.

Competing interests

The authors declare that they have no competing interest.

Financial Disclosure

All authors declare no financial support.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. This study was approved by the Institutional Review Board at our institutes.

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