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ประสิทธิภาพของการใช้ค่า apparent diffusion coefficient ของ diffusion-weighted magnetic resonance imaging ประเมินความสามารถในการวินิจฉัยก้อนเนื้อร้ายแรงในตับ

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The Performance of the Diffusion-Weighted Magnetic Resonance Imaging using Apparent Diffusion Coefficient Measurement in Detecting Malignant Liver Lesions

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หลักการและวัตถุประสงค์: ค่า ADC (Apparent diffusion coefficient) สามารถอธิบายลักษณะของก้อนเนื้อในตับ การศึกษาก่อนหน้านี้มีความแตกต่างของค่า ADC ที่เหมาะสมในการแยกระหว่างก้อนเนื้อไม่ร้ายแรงและก้อนเนื้อร้ายแรงในตับ การศึกษาครั้งนี้มีวัตถุประสงค์ เพื่อวัดค่า ADC ของก้อนเนื้อร้ายแรงในตับและระบุจุดตัด ADC ที่เหมาะสมในการวินิจฉัยแยกระหว่างก้อนเนื้อไม่ร้ายแรงและก้อนเนื้อร้ายแรง

วิธีศึกษา: เป็นการศึกษาย้อนหลังโดยการเปรียบเทียบค่า ADC ของ 180 รอยโรคของตับที่ได้รับตรวจวินิจฉัยโรคด้วยคลื่นแม่เหล็กไฟฟ้า (MRI; Magnetic resonance imaging) (ระหว่างวันที่ 1 มิถุนายน 2555 ถึงวันที่ 31 ธันวาคม 2557 พร้อมหาค่าจุดตัด ADC เพื่อแยกระหว่าง ก้อนเนื้อไม่ร้ายแรงและก้อนเนื้อร้ายแรงในตับ

ผลการศึกษา: ก้อนเนื้อร้ายแรงในตับ 79 รอยโรค (CCA (Cholangiocarcinoma) 52, HCC (hepatocellular carcinoma) 20, liver metastastais 7) มีค่าเฉลี่ย ADC เท่ากับ 1.06x10-3 มม^2/วินาที และก้อนเนื้อไม่ร้ายแรงในตับ 101 รอยโรค (hemangioma 44, FNH 11, hepatic adnoma 7, cyst 39) มีค่าเฉลี่ย ADC เท่ากับ 1.93x10-3 มม^2/วินาที ซึ่งมีความ

Background and Objective: ADC (Apparent diffusion coefficient) values have been shown to be helpful for liver lesion characterization. There are; however, discrepancies in the ADC values and controversies regarding the optimal cutoff ADC values to differentiates malignant from benign liver lesions. The purpose of this study was to measure ADC values of malignant liver lesions and to identify the optimal cutoff ADC value to differentiate malignant from benign liver lesions.

Material and Methods: A retrospective study of 180 MRI (Magnetic resonance imaging) of liver during June 1, 2012 to December 31, 2014. ADC value was measured and compared between benign and malignant liver lesions. The optimal ADC value to differentiated between malignant and benign liver lesions was calculated.

Results: Seventy-nine malignant liver lesions included 52 CCAs, 20 HCCs, 7 liver metastases had

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แตกต่างอย่างมีนัยยะสำคัญทางสถิติ (p<0.05) จุดตัดค่า ADC ที่เหมาะสมในการวินิจฉัยก้อนเนื้อร้ายแรงคือ 1.49x10-3 มม^2/วินาที ด้วย sensitivity 84.8%, และ specificity 81.2%
สรุป: ค่า ADC ของก้อนเนื้อร้ายแรงมีค่าน้อยกว่าก้อนเนื้อไม่ร้ายแรงในตับอย่างมีนัยยะสำคัญทางสถิติ จุดตัดค่า ADC ที่เหมาะสมในการวินิจฉัยแยกโรคของก้อนเนื้อร้ายแรงในตับเท่ากับ 1.49x10-3 มม^2/วินาที

คำสำคัญ: การถ่ายภาพด้วยคลื่นสนามแม่เหล็ก(MRI); ค่าสัมประสิทธิ์การแพร่กระจายที่ชัดเจน(ADC); มะเร็งท่อน้ำดี (CCA); มะเร็งตับ (HCC); การแพร่กระจายของตับ

median ADC value 1.06x10^{-3} mm^2/sec. 101 benign liver lesions included 44 hemangiomas, 11 FNHs, 7 hepatic adenomas and 39 cysts had median ADC value 1.93x10^{-3} mm^2/sec. The differences between the median ADC values of malignant liver lesions (1.06x10-3 mm^2/sec) and benign liver lesions (1.93x 10^{-3} mm^2/sec) was statistically significant (p<0.05). The ADC value of <1.49x10^{-3} mm^2/sec was the optimal cut-off values to indicate malignant liver mass with the sensitivity of 84.8%, specificity of 81.2%.
Conclusion: ADC value is useful for differentiating malignant from benign liver lesions with1.49x10^{-3} mm^2/s as optimal cutoff ADC value.

Keyword: Magnetic resonance imaging (MRI); Apparent diffusion coefficient (ADC) value; Cholangiocarcinoma (CCA); hepatocellular carcinoma (HCC); liver metastasis; hemangioma; focal nodular hyperplasia (FNH); hepatic adenoma; cyst

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Introduction

The differential diagnosis of malignant and benign liver lesions remains a diagnostic challenge, especially in patients who cannot receive MRI contrast owing to contrast allergy, or renal insufficiency. Diffusion-weighted imaging (DWI) can be useful in these patients by providing additional formation and hence DWI is increasingly being used for tumor detection and characterization[1]. Recently, some studies have reported that the ADC values, which is one of the calculated parameters of DWI might be useful for differential diagnosis of benign and malignant lesions in the liver[2-23]. ADC values in malignant lesions tend to decreased, probably due to increased tissue cellularity or cell density. In addition to cellular membranes, intracellular cytoskeleton, organelles, matrix fibers and soluble macromolecules contribute to diffusion restriction in tumors[24]. As ADC in malignant lesions are lower, [2-9, 12,13, 16-21, 25-28] quantitative assessment of ADC measurement as a biomarker has the potential to differentiate malignant and benign liver tumors.

Kim et al.[4] used of a threshold ADC of 1.6x10^{-3} mm^2/sec for differentiation of malignant liver lesions from benign lesions, with a sensitivity of 98% and a specificity of 80%. Similar to Taouli et al.[5] used of threshold ADC of 1.5x10^{-3} mm^2/sec for the diagnosis of malignant lesions would result in sensitivity and specificity of 84% and 89%, respectively. Whereas, Ichikawa et al.[6] suggested the cutoff ADC value is 5.5x10^{-3} mm^2/sec for malignant tumor distinguishes from hemangiomas, with a sensitivity and a specificity of 94% and 100% [10], respectively.

However, there are considerable discrepancies in the ADC values in previous reports[2-7, 27], and there is still controversy about the optimal cutoff ADC value to differentiates malignant from benign liver lesions [2-4, 6-8].

The purpose of the study are to determine the performance of the DWI using ADC measurement in detecting malignant liver lesions and to identify the optimal cutoff ADC value to differentiates malignant from benign liver lesions.

Materials and Methods

Patients

Our retrospective study was approved by the institutional review board.

During June 1, 2012 to December 31, 2014 all MRI studies with focal liver lesions were included. Inclusion criteria in the study were (1) All pathological proven the largest focal liver lesions more than 10 mm in each MRI (2) The focal liver lesions without a history of any treatment and (3) The largest benign focal liver lesions with classical MRI findings in each MRI

studies which follow-up examinations using US, CT or MRI at least 6 months duration. The exclusion criteria were all lesions with low images quality of DWI and ADC map. The lesions were classified into benign or malignant groups.

MRI

MR imaging

MR imaging was performed on a 1.5-T system (MagnetomAera, Siemens Medical Solutions, Erlangen, Germany) with sixteen channel body phased array coils anterior and two spine clusters (three channels each) posterior.

Coronal T2-weighted half-Fourier single-shot turbo spin-echo (HASTE) sequence and an axial T2-weighted turbo spin-echo sequence were acquired as well as an axial dynamic T1-weighted, three-dimensional spoiled gradient-recalled echo sequence (volumetric interpolated breath-hold examination (VIBE) sequence with spectral fat saturation) following the intravenous administration of Gd-DTPA.

DWI were acquired using a single-shot echo-planar imaging sequence. Thus, the gradient factors (b values) were 0, 150, and 800 s/mm^2. The technical parameters were as follows: echo time, 65 ms; EPI factor, 125; echo spacing, 0.77 ms; receiver bandwidth, 1736 Hz/pixel; spectral fat saturation; field of view, 292 × 360 mm; matrix, 125 × 192; section thickness, 6 mm. For shortening of the echo train length, integrated parallel imaging techniques (iPAT) by means of generalized autocalibrating partially parallel acquisitions (GRAPPA) with a twofold acceleration factor were used. For respiratory triggering, PACE (prospective acquisition correction) was implemented. Data were acquired during the end-expiratory phase. DWI was performed before the administration of Gd-DTPA.

Procedure

All MRI images of the patients who were eligible in this study were reviewed. Demographic data included age, gender, diagnosis (benign and malignant), subtypes of diagnosis (HCC, CCA, liver metastasis, cyst, hemangioma, FNH, and adenoma) were collected. The ADC measurement of liver masses was measured from ADC maps.

Image analysis

All MR images were analyzed retrospectively by a radiologist specialized in gastrointestinal imaging with more than 9 year experienced. All lesions equal or larger than 1 cm were selected to avoid volume errors and underwent 3 measurements per lesion and then averaging them to get the final ADC of each lesion. Malignant lesions with necrotic or fibrous core were measured only solid portion to void heterogeneous ADC value. The largest lesion was selected in patient who has multiple similar characteristic pathology.

Statistical analyses

Demographic data variables which included baseline characteristics were divided into dichotomous or polytomous variables. All variables were summarized using descriptive statistic presentation in percentage, mean and standard deviation. However, if the distribution of this data was not a normal distribution, then median and inter-quartile range were used instead. Wilcoxson signed rank test was used to analysis the differences between the ADC values of benign and malignant liver mass. The ROC curve was used to summarize the overall accuracy of the DWI using ADC measurement for detecting malignant liver mass. Then an optimal cut-off point was determined. The performance of the test was summarized by the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), likelihood and Youden'sindex.

Sample size calculation

Sample size calculation is based on the objective of the study which was the performance of the DWI using ADC measurement in detecting malignant abdominal mass. ROC curves are used to summarize the accuracy of diagnostic tests. Therefore, calculating sample size was based on the area under the ROC curve (AUC) according to the methodology of Hanley and McNeil (1983)[29].

This method varies the sample size until a sufficiently small S.E. of the area under the ROC curve is achieved. The sample size of at least 70 cases were enough and feasible to conduct in clinical practice at the SE of $p<0.05$.

Results

Baseline data

During a studied period, there were 180

consecutive focal liver lesions included. The baseline and characteristics of lesions are demonstrated in Table 1.

The 79 malignant lesions were pathological proven by surgery or biopsy composed with 52 CCAs, 20 HCCs and 7 liver metastases. There were 101 eligible benign liver lesions are included in the study. In 44 hemangiomas, the diagnosis was pathologically confirmed by surgery only 1 lesion and the other 43 lesions were based on typical MRI findings and follow up images. In 39 cysts, the diagnosis was based on typical MRI findings and follow up serial CT or MRI examination at least 6 months (range, 6-23 months). In 11 FNHs, 4 lesions were histopathologically confirmed with surgery and the other 7 lesions base on typical MRI findings criteria using hepatocyte-specific contrast agents. In all 7 adenomas, the diagnosis was based on typical MRI findings criteria using hepatocyte-specific contrast agents.

The ADC values

The median ADC value of 101 benign liver lesions was 1.93x10^{-3} mm^2/sec (IQR1-3= 1.57x10^{-3} mm^2/sec-2.70x10^{-3} mm^2/sec) while the median ADC value of 79 malignant liver lesions was 1.06x10^{-3} mm^2/sec (IQR1-3= 0.92x10^{-3} mm^2/sec-1.33x10^{-3} mm^2/sec). The median ADC value of malignant liver lesions differs significantly from benign liver lesions ($p<0.05$). Figure 1 shows the distribution of the ADC values of benign and malignant liver lesions and Figure 2 shows the median ADC values by subtypes of liver lesion.

Table 1 Baseline characteristics of studied populations

Variables	N=180
Age; years, median (IQR1, IQR3)	56.5 (51, 65)
Male sex (%)	91 (50.6)
Diagnosis	
Benign lesion (%)	101 (56.1)
Cyst	39 (21.6)
Hemangioma	44 (24.5)
FNH	11 (6.1)
Adenoma	7 (3.9)
Malignant mass (%)	79 (43.9)
Liver metastasis	7 (3.9)
HCC	20 (11.1)
CCA	52 (28.9)

Note; N: total number of liver lesions, IQR: inter-quartile range, FNH: focal nodular hyperplasia, HCC: hepatocellular carcinoma, CCA: cholangiocarcinoma

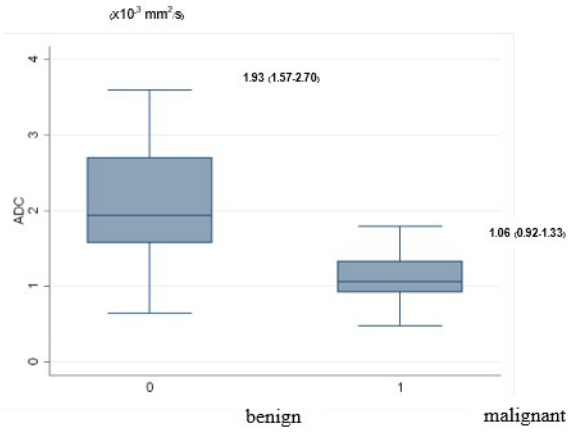

Figure 1 The median ADC values of benign and malignant liver lesions.
Note; Median ADC and interquartile range 1-3 of each lesion were presented in the figure.

The performances of the ADC value to detect malignant liver lesions

The area under the ROC curve (AUC) of ADC value to indicate malignant liver mass was 0.9(95% confidence interval (CI) 0.87, 0.95) as shown in Figure 3. Tables 2 demonstrates the performance of the ADC value at different cutoff points to predict malignant liver mass.

The ADC values and their performances to detect malignant liver lesions from solid benign liver lesions (including FNHs and adenomas)

According to the Wilcoxson rank-sum test, the median ADC value of malignant liver lesions were no

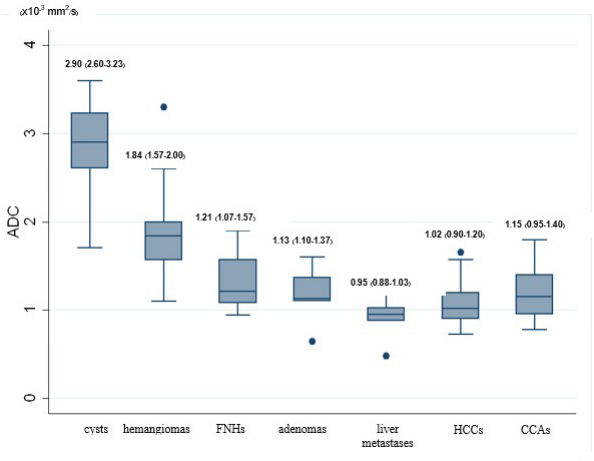

Figure 2 The distribution of ADC by subtypes of diagnosis.
Note; Median ADC and interquartile range 1-3 of each lesion were presented in the figure.

Table 2 The performance of the ADC for detecting malignant liver lesions based on ROC curve analysis

Cut point	Sensitivity	Specificity	PPV	NPV	LR+	LR-	AUC	Youden's index
<1.48	83.5	81.2	77.6	86.3	4.44	0.2	0.82	0.65
<1.49	84.8	81.2	77.9	87.2	4.51	0.19	0.83	0.66
<1.5	84.8	81.2	77.9	87.2	4.51	0.19	0.83	0.66
<1.51	86.1	79.2	76.4	87.9	4.14	0.18	0.83	0.65
<1.52	86.1	78.2	75.6	87.8	4.0	0.18	0.82	0.64

Note: PPV; positive predictive value, NPV; negative predictive value, LR+; positive likelihood ratio, LR-; negative likelihood ratio, AUC; area under the ROC curve, Youden's index; J = Sensitivity + Specificity – 1(Its value ranges from 0 to 1, a value of 1 indicates that there are no false positives or false negatives, i.e. the test is perfect.

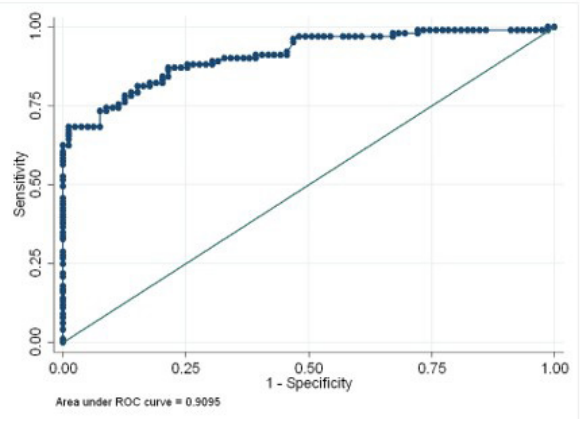

Figure 3 ROC curve analysis of ADC to determine malignant liver lesions.

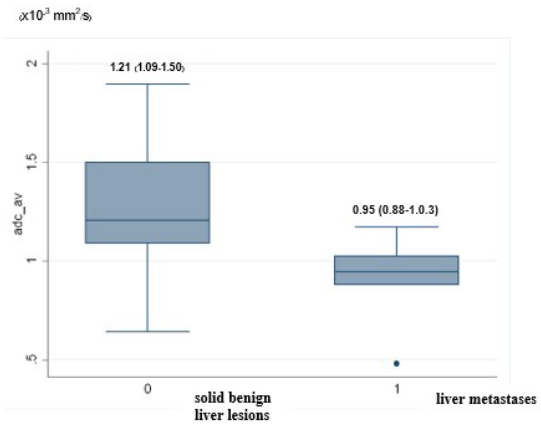

Figure 4 The median ADC values of solid benign liver lesions and liver metastases.
Note; Median ADC and interquartile range 1-3 of each lesion were presented in the figure.

significantly different from solid benign liver lesions (p=0.06).

The ADC values and their performances to detect liver metastases from solid benign liver lesions (including FNHs and adenomas)

According to the Wilcoxson rank-sum test, the median ADC value of liver metastases differs significantly from solid benign liver lesions (p<0.05). Figure 4 shows the distribution of the ADC values of solid benign liver lesions and liver metastases.

The area under the ROC curve (AUC) of ADC value to indicate liver metastases was 0.86 (95%CI 0.7 - 1.0) as shown in Figure 5. Table 3 demonstrates the performance of the ADC values at different cutoff points to predict hepatic metastases from solid benign liver lesions.

Discussion

Many preliminary studies have measured the ADCs of the liver lesions with diffusion-weighted echoplanar MR imaging and have demonstrated lower ADC values in malignant than in benign lesions, some of them reported overlap values. Miller et al.[8] reported the more common benign liver lesions were hemangiomas and cysts, had significantly higher mean ADC values compared to other lesions. Similar to this study, cyst was the most common liver lesions, fol-

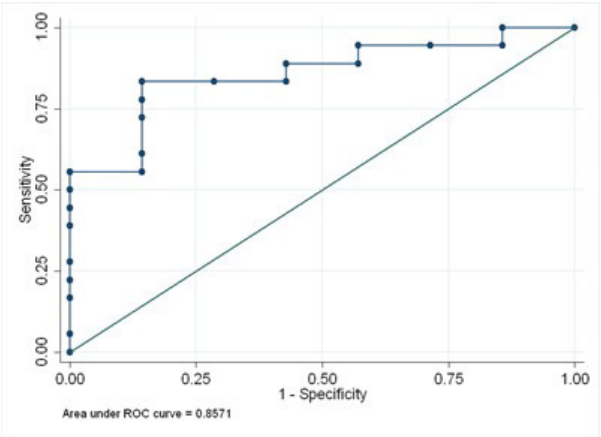

Figure 5 ROC curve analysis of ADC to determine liver metastases.

Table 3 The performance of the ADC for detecting liver metastases from solid benign liver lesions based on ROC curve analysis

Cut point	Sensitivity	Specificity	PPV	NPV	LR+	LR-	AUC	Youden's index
< 1.02	71.4	83.3	62.5	88.2	4.28	0.34	0.77	0.55
<1.04	85.7	83.3	66.7	93.8	5.13	0.17	0.85	0.69
<1.06	85.7	83.3	66.7	93.8	5.13	0.17	0.85	0.69
<1.08	85.7	77.8	60.0	93.3	3.86	0.18	0.82	0.64
<1.1	85.7	72.2	54.5	92.9	3.08	0.20	0.79	0.58

Note: PPV; positive predictive value, NPV; negative predictive value, LR+; positive likelihood ratio, LR-; negative likelihood ratio, AUC; area under the ROC curve, Youden's index; J = Sensitivity + Specificity – 1(Its value ranges from 0 to 1, a value of 1 indicates that there are no false positives or false negatives, i.e. the test is perfect.

lowed by hemangiomas. Liver cysts and hemangiomas were also higher in ADC values than other lesions, most likely secondary to their higher fluid content resulting in more free water molecule diffusion.

In contrast, solid lesions show the low ADC values likely due to their high cellularity and the resultant restricted diffusion of water molecules. Hemangiomas are not pure fluid-containing lesions but can contain vascular endothelial tissue, fibrous septa, and blood. These non-fluid elements do restrict water motion and consequently ADC values of hemangiomas are lower than that of cysts as seen in our study. The median ADC value of cyst and hemangioma in our study were $2.91.04x10^{-3}$ mm^2/s and $1.841.04x10^{-3}$ mm^2/s, respectively.

The result of this study suggested the optimal cutoff ADC value for distinction between malignant and benign liver lesions was $1.49x10^{-3}$ mm^2/s (when using a maximum b value of 800 s/ mm^2), with sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of 84.8% , 81.2%, 4.51, and 0.19, respectively).

This study reported lower sensitivity and lower specificity than Chen et al.[10], a meta-analysis stud found DWI was useful for differentiating between malignant and benign hepatic lesions with sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of 93% (95% confidence interval (CI): 0.91-0.95), 87% (95% CI: 0.83-0.91), 7.28 (95% CI: 4.51-11.76), and 0.09 (95% CI: 0.05-0.17), respectively. They mentioned the diagnostic capability might be overestimated due to the possibility of selection bias.

The optimal cutoff ADC value of this study was closed to the results of Kim et al.[4] ($1.6x10^{-3}$ mm^2/s when using a maximum b value of 846 s/ mm^2), Taouli et al.[5] ($1.5x10^{-3}$ mm^2/s, maximum b value of 500 s/ mm^2), Miller et al.[8] ($1.5x10^{-3}$ mm^2/s, maximum b value of 500 s/ mm^2), and Gourtsoyianni et al.[2] ($1.47x10^{-3}$ mm^2/s, maximum b value of 1,000 s/ mm^2), whereas the results of Ichikawa et al.[6] is $5.5x10^{-3}$ mm^2/s when using a maximum b value of 55 s/ mm^2. The similarity or difference between cutoff ADC values should be due to the magnitude of the maximum b value used for the other studies, as discussed in the preceding text. Ichikawa et al.[6] mentioned in their report that larger b factor, those greater than 400 s/ mm^2 should be chosen for more precise evaluation of ADCs in the abdomen, but the image quality of a diffusion-weight image with greater b values would be greatly diminished because the T2 relaxation time of abdominal tissues is short. However, Kim et al.[4] mentioned in their report that greater b values can be used for characterizing liver lesions because the targets for characterization should be the lesions, which have long T2 relaxation time and show high signal intensity on T2-weighted images. Moreover, ADCs of liver lesions measured with larger b values would be less affected by the magnitude of the maximum b value and would be more similar to a diffusion coefficient less affected by perfusion. In agreement with Kim et al.[4] and Ichikawa et al.[6], we selected b 800 s/mm^2 factors to obtain diffusion-weight images in this study.

Due to the fact that solid benign liver lesions, including FNH and adenoma, being hypercellular lesions, are expected to present with low ADC values. The prior study of Miller et al.[8] and Sandrasegaran, et al.[9] reported some overlaps in ADC values between solid benign liver lesions (FNHs and adenomas) and malignant lesions. Our results similar to previous reports which no significant difference between overall ADC value of malignant and solid benign liver lesions.

However, 1.04x10^{-3} mm^2/s value of ADC was used to be the optimal cut off ADC value to differentiated liver metastases from solid benign liver lesions, with a sensitivity and a specificity (85.7%, and 83.3%, respectively) that similar sensitivity and specificity of meta-analysis of Wei et al.[11], who reported DWI was useful for differentiation between liver metastases and benign focal liver lesion with sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of 87%, 90%, 8.50, and 0.17, respectively. The cut off ADC value in our study was lower than study of Testa et al.[30], who reported 1.2x 10^{-3} mm^2/s was the ADC cut off value to differentiate between solid benign and malignant liver lesion with a sensitivity of 71%, and a specificity of 71%.

We also found no significant difference between ADC value of the primary and metastasis liver malignancy which is similar to reported of Goya et al.[31], who found ADC value are not helpful in differentiation between HCCs (1.06x10^{-3} mm^2/s) and liver metastases (1.102x10^{-3} mm^2/s). Among the primary liver tumor CCA is the largest number of primary liver tumor because the study population live in the northeast of Thailand where it has the highest incidence of CCA[32]. The median value for ADC of CCA was 1.15x10^{-3} mm^2/s which is lower than the study of Xing-Yu Cui et al.[33], who found the mean value for ADC of extrahepatic CCA was 1.31 ± 0.29x10^{-3} mm^2/s.

Our study has few potential limitations. First, the single-shot echoplanar images contain a distortion artifact caused by the susceptibility effect, which tends to be more severe with a larger b value. This advantage may be reduced in the future if it becomes possible to obtain diffusion-weighted images with other fast imaging sequences that are less sensitive to the effects of static magnetic field inhomogeneities. Second, we did not have histopathologically confirmed diagnosis for all patients or lesions; however, those without surgery or biopsy-proven lesions were only included in the study if they has typical features on MR images as well as adequate follow-up to confirm the diagnosis.

Conclusion

In conclusion, ADC value is useful for differentiating malignant from benign liver lesions using 1.49x10^{-3} mm^2/s optimal cutoff ADC value and 1.04x10^{-3} mm^2/s optimal cutoff ADC value to differentiated metastases from benign solid liver lesions.

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