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FULL PAPER

Prediction of histological grade of hepatocellular carcinoma using quantitative diffusion-weighted MRI: a retrospective multivendor study

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Objective: To evaluate the usefulness of quantitative diffusion-weighted (DW) imaging acquired by multivendor magnetic resonance units for predicting grade of hepatocellular carcinoma (HCC).

Methods: 83 patients with 100 histologically diagnosed HCCs who underwent pre-operative liver DW imaging with $b = 0$ and 1000 s mm^{-2} or $b = 0$ and 800 s mm^{-2} at any of six institutions were included. Two radiologists independently measured the apparent diffusion coefficient (ADC) of the lesion as well as non-ADC parameters, such as the relative contrast ratio and the contrast-to-noise ratio (CNR) between the lesion and the liver parenchyma on high b -value DW images. The diagnostic performance of the DW parameters in discriminating poorly-differentiated HCCs was compared using receiver operating characteristic (ROC) analysis.

Results: The areas under the receiver operating characteristic curves for the CNR (86.4% [95% confidence interval (CI) (77.2–95.6)] and 83.9% [95% CI 71.2–96.6] for $b = 1000$ and 800 s mm^{-2} , respectively) and the relative contrast ratio (85.3% [95% CI 75.5–94.8] and 83.5% [95% CI 70.5–96.4]) tended to be superior to the ADC [71.1% [95% CI (56.9–85.2)] and 75.7% [95% CI (55.1–96.2)]; $p < 0.05$ for CNR vs ADC for $b = 1000 \text{ s mm}^{-2}$, but not significant for other parameters) for discrimination of poorly-differentiated HCCs.

Conclusion: All DW parameters could discriminate HCC grade. Non-ADC parameters might be more useful than the ADC for predicting poorly-differentiated HCCs.

Advances in knowledge: The utility of quantitative DW parameters for predicting HCC grade was demonstrated by using multivendor MR units.

INTRODUCTION

Histological grade is one of the prognostic factors in patients with hepatocellular carcinoma (HCC).^{1–4} Metastases and recurrences after liver resection and transplantation are seen more frequently in poorly-differentiated HCC (pHCC).^{5–11} The grade of HCC has a relationship with the effectiveness of radiofrequency ablation and the survival rate thereafter.^{1,12} Accurate radiological stratification of HCC grade is helpful for predicting the prognosis and selecting the therapeutic strategy.

The ability of MRI to predict histological grade of HCC has been evaluated using various methods. Gadolinium

ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced MRI or diffusion-weighted imaging (DWI) has been used to discriminate the grade of HCC in most of the recent studies. The grade is qualitatively predictable to some extent by the enhancement pattern of the lesion, its size, and the degree of necrosis.¹³ However, in terms of quantitative analysis, the ability of gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced MRI to discriminate pHCCs from other HCCs is inadequate.^{14–17} The apparent diffusion coefficient (ADC), which is the most commonly used index in DWI, has been used for quantitative assessment of malignant tumours. Several studies have evaluated the correlation between the ADC and histological grade of

HCC.^{17–27} but yielded conflicting results. Recently, some studies showed that non-ADC parameters, *i.e.* the relative contrast ratio (RCR) or contrast-to-noise ratio (CNR) of HCC to the surrounding liver parenchyma on DW images, were superior to the ADC in predicting the grade of HCC.^{18,19,21} However, they were single-centre studies using single MR units, and the interobserver reproducibility of these measurements has not been reported.

The aim of this study was to evaluate the usefulness and the reproducibility of DW parameters, including RCR, CNR and ADC using multivendor MR units for predicting grade of HCC.

METHODS AND MATERIALS

Patients

This multicentre, retrospective, multivendor study included patient data from six institutions (A, Medical Hospital of Tokyo Medical and Dental University; B, Ome Municipal General Hospital; C, Ochanomizu Surugadai Clinic; D, Advanced Imaging Center Yaesu Clinic; E, Japanese Red Cross Musashino Hospital; F, Medical Scanning Ochanomizu). The study protocol was approved by the institutional review boards at institutions A, B and E. Institutions C, D and F did not have ethical review committees, so delegated approvals to Institution A. The requirement for informed consent was waived.

We identified 131 consecutive patients with HCC that was histologically diagnosed after liver resection in Institution A from January 2010 to December 2016 who underwent pre-operative liver DW MRI acquired in the axial plane at $b = 0$ s mm⁻² and a high b -value (1000 s mm⁻² or 800 s mm⁻²). Patients were excluded if the quality of DWI was poor ($n = 8$), if the diameter of their HCC was less than 1.5 cm because of decreasing reliability of

signal intensity (SI) measurement ($n = 14$), and if their HCC had already been treated with radiofrequency ablation, transcatheter arterial chemoembolization, or chemotherapy before MRI examination or surgery ($n = 26$). We finally enrolled 83 patients with 100 HCCs.

Table 1 shows the patients' demographic and tumour characteristics. All patients were classified as having Child–Pugh class A disease. The HCCs were classified as well-, moderately-, or poorly differentiated according to the criteria of the Liver Cancer Study Group of Japan.²⁸ When a HCC had multiple histological features, it was classified as the higher grade if the area of that grade accounted for over 10% of the entire tumour.

MRI

The average time interval between pre-operative liver MRI and surgery was 41.0 days on $b = 0$ and 1000 s mm⁻² (range, 2–134 days) and 42.7 days on $b = 0$ and 800 s mm⁻² (range, 12–126 days) ($p = 0.40$). MRI examinations were performed on 1.5 T or 3.0 T MR units (1.5 T, Signa HDxt [GE Medical Systems, Milwaukee, WI] and Intera Achieva NovaDual [Philips Medical Systems, Best, Netherlands]; 3.0 T, Ingenia [Philips] and SPECTRA [Siemens Medical Solutions, Erlangen, Germany]). Table 2 shows the MR units at the institutions and their DWI protocols.

Imaging analysis

The MRI data were evaluated using a Digital Imaging and Communications in Medicine viewer (OsiriX imaging software v. 8.0; OsiriX Foundation, Geneva, Switzerland) by two board-certified radiologists (YO and YI, with 7 and 10 years of experience in liver MRI, respectively) who worked independently and were blinded to the histological grade of HCC. Three oval regions of interest (ROIs) were placed on the “solid” areas where

Table 1. Patient demographic and tumour characteristics

Parameter	$b = 1000$ s mm ⁻² (Institutions A–D)	$b = 800$ s mm ⁻² (Institutions E, F)	p -value
Mean age (y) ^a	68.4 ± 11.0	69.6 ± 11.0	0.59
Sex (male/female)	41/8	25/9	0.28
Background liver			
Hepatitis B virus	12	8	1.00
Hepatitis C virus	13	13	0.34
Alcoholism	13	5	0.28
Resected tumours (single/multiple)	45/4	29/5	0.48
Tumour locations (right/left)	36/22	33/9	0.08
Subdiaphragmatic locations (right/left)	13/6	11/2	1.00/1.00
Histological tumour grade (well-/moderately-/poorly-differentiated)	8/31/19	10/20/12	0.50
Mean tumour diameter (mm) ^a	44.0 ± 30.4	43.3 ± 29.2	0.99
Median AFP level (ng ml ⁻¹) ^b	5.2 (1.5–484000)	17.9 (1.3–15682)	0.028
Median PIVKA-II level (mAU ml ⁻¹) ^b	51.0 (10–77800)	221.5 (17–239630)	0.0055

AFP, alpha-fetoprotein; PIVKA, protein induced by Vitamin K absence or antagonists.

^aThe data are shown as the mean ± standard deviation.

^bThe data are shown as the median with the range in parentheses. All AFP and PIVKA-II levels were measured in Institution A before surgery.

Table 2. MR units in the six institutions and their DWI protocols

Institution	A	B	C	D	E	F
MR unit	GE Signa HDxt	Philips Intera Achieva NovaDual	Philips Intera Achieva NovaDual	Philips Ingenia	GE Signa HDxt	Siemens Spectra
Coil	8-ch body upper	32 cm SENSE/torso cardiac coil	32 cm SENSE/torso Cardiac coil	16-ch dStream Torso coil	8-ch body Upper	6-ch body coil + pine coil
Magnetic field strength (T)	1.5	1.5	1.5	3	1.5	3
b factor (s mm^{-2})	1000	1000	1000	1000	800	800
Repetition time (ms)	4500	1198.3–1336.7	2319–5000	6250	5500	1,3800
Echo time (ms)	76.3	73	69	65	72.5	68
Acquisition matrix	88×110	112×88	144×114	128×135	128×192	128×63
Image matrix	256×256	256×256	256×256	384×384	256×256	256×168
Field of view (cm)	40	35	35–40	36	40	38
Slice thickness (mm)	7	8	7–11	6–7.5	6	6
Slice gap (mm)	2	2	0.7–1.1	0–1	2	0
Respiratory motion compensation technique	Respiratory-triggered	Respiratory-triggered	Respiratory-triggered	Free-breathing	Respiratory-triggered	Free-breathing
Fat suppression	CHESS	CHESS	CHESS	CHESS + SSGR	CHESS	CHESS + SSGR

DWI, diffusion-weighted imaging; CHESS, chemical shift selective; SSGR, section-select gradient reversal.

Figure 1. Images from a 64-year-old male with a HCC measuring 9.0 cm in diameter, classified as poorly-differentiated. This tumour was composed mainly of moderately-differentiated HCC coexisting with poorly-differentiated HCC that accounted for over 10% of the entire tumour area. A 1.5 T magnetic resonance unit was used and diffusion-weighted images were acquired on $b = 0$ and 800 s mm^{-2} . (a) Diffusion-weighted image, (b) T_2 weighted image using a fast spin echo sequence, (c) a three-dimensional T_1 weighted image using a gradient-recalled echo sequence with fat suppression (3D-FST₁WI) during the arterial phase, and (d) a 3D-FST₁WI during the hepatobiliary phase. Oval regions of interest are placed on the “solid” area where the signal intensity is considered to be highest on DWI at a high b -value and on the surrounding normal hepatic parenchyma. We avoided placing regions of interest in a necrotic part of this lesion (arrow). The measurements obtained were as follows: apparent diffusion coefficient, $0.85 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$; relative contrast ratio, 10.9; and contrast-to-noise ratio, 80.1. DWI, diffusion-weighted imaging; HCC, hepatocellular carcinoma.

the SI values were considered to be the three highest in DWI on $b = 1000 \text{ s mm}^{-2}$ or 800 s mm^{-2} (Figure 1). Necrotic, haemorrhagic and cystic lesions were avoided by referring to other sequences. The ROIs were copied and pasted on the same locations in DWI on $b = 0 \text{ s mm}^{-2}$. Three round ROIs with a diameter of 10 mm were then set on the normal hepatic parenchyma near the three lesions in DWI on a high b -value, excluding visible large vessels by reviewing the other MR sequences.

The ADC, RCR and CNR on DWI were calculated as follows: $\text{ADC} = \ln [\text{SI (lesion on } b = 0 \text{ s mm}^{-2}) / \text{SI (lesion on high } b\text{-value [1000 or } 800 \text{ s mm}^{-2}])}] / 1000 \text{ or } 800$; $\text{RCR} = \text{SI (lesion on high } b\text{-value)} / \text{SI (liver on high } b\text{-value)}$; and $\text{CNR} = [\text{SI (lesion on high } b\text{-value)} - \text{SI (liver on high } b\text{-value)}] / \text{noise (liver on high } b\text{-value)}$, where $\ln$ is the natural logarithm, the SI used in the RCR and CNR calculations is the mean SI of the 3 ROIs on each high b -value, and noise is the mean standard deviation of the SI of the 3 ROIs. The ADC was calculated at each ROI, and the mean ADC of the 3 ROIs was used for further analyses.

Statistical analysis

The statistical analysis was performed using R v. 3.3.1 software (R Foundation for Statistical Computing, Vienna, Austria). The patients were divided into two groups according to the b -values (0 and 1000 s mm^{-2} or 0 and 800 s mm^{-2}) used for DWI acquisition. Differences between two quantitative variables were tested for significance using the Wilcoxon rank sum test. Qualitative MR variables were tested using Fisher's exact test.

The relationships between histological grade of HCC and DW parameters were assessed using the Spearman's rank correlation test, after which a correlation coefficient (ρ) was obtained for each b -value group. The degree of ρ was defined as follows: none (0.00 – 0.20), weak (0.21 – 0.40), moderate (0.41 – 0.70), or strong (0.71 – 1.00). A positive ρ -value was interpreted as a positive correlation and a negative ρ -value as a negative correlation. The Kruskal–Wallis test was used to assess for statistically significant differences in values for the DW parameters among the HCC grades, and subsequent pairwise comparisons were performed using the Wilcoxon rank sum test with Bonferroni correction. The diagnostic performance of the parameters in discriminating the grades; (1) well-differentiated HCCs (wHCCs) vs moderately-differentiated HCCs (mHCCs) and pHCCs, and (2) pHCCs vs wHCCs and mHCCs, was evaluated for each group using receiver operating characteristic (ROC) analysis. The areas under the ROC curves (AUCs) of the parameters for discriminating pHCCs from non-pHCCs, *i.e.* wHCCs and mHCCs were compared for statistical significance using the pROC package in R. The optimal cut-off values were chosen to minimize the $(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$ formula or to be the point closest to the top left part of the plot.²⁹ When no significant difference was found between the paired AUCs, the power of the test ($1 - \beta$) was calculated as a *post hoc* analysis.

In addition, the DW parameters for each grade were compared between $b = 1000 \text{ s mm}^{-2}$ and $b = 800 \text{ s mm}^{-2}$ using the Mann–Whitney U test.

Differences in the DW parameters between the institutions were evaluated for each b -value group and were stratified by grade, sensitivity and specificity for discriminating pHCCs. The values for the DW parameters at four institutions on $b = 0$ and 1000 s mm^{-2} were analysed using the Kruskal–Wallis test and at two institutions on $b = 0$ and 800 s mm^{-2} using the Mann–Whitney U test; sensitivity and specificity values were assessed using Fisher's exact test.

The interobserver agreement values for the ADC, RCR and CNR were assessed using the intraclass correlation coefficient (ICC) and the Bland–Altman method. The ICC was graded as follows: poor (0.00 – 0.20), fair (0.21 – 0.40), moderate (0.41 – 0.60), strong (0.61 – 0.80), or almost perfect (0.81 – 1.00). The mean absolute difference (bias) and the 95% confidence interval (CI) of the mean difference (limits of agreement) between the two radiologists' measurements were obtained using the Bland–Altman method.

A p -value of less than 0.05 indicated a statistically significant difference.

RESULTS

Relationships between histological grade and DW parameters

Figure 2 and Table 3 show the relationship between the histological grades of HCC and DW parameters.

The ADC on $b = 0$ and 1000 s mm^{-2} (ADC_{1000}) showed a weak negative correlation with grade of HCC ($\rho = -0.27$, $p = 0.041$), and the ADC on $b = 0$ and 800 s mm^{-2} (ADC_{800}) showed no correlation ($\rho = -0.44$, $p < 0.01$). The RCR and CNR on $b = 1000 \text{ s mm}^{-2}$ (RCR_{1000} and CNR_{1000}) or 800 s mm^{-2} (RCR_{800} and CNR_{800}) showed moderate positive correlations ($\rho = [0.51$ – $0.62]$, $p < 0.001$).

In multiple comparisons between the histological grades, there was a significant difference in the ADC_{1000} between mHCCs and pHCCs ($p = 0.003$) and a significant difference in the ADC_{800} between wHCCs and pHCCs ($p = 0.019$). Significant differences in RCR and CNR were found between pHCCs and the other grades of HCC ($p < 0.001$ for $b = 1000 \text{ s mm}^{-2}$ and $p < 0.05$ for $b = 800 \text{ s mm}^{-2}$).

Figure 3 shows the results of the ROC curve analysis for DW parameters on each high b -value for discriminating pHCC. The AUCs of RCR_{1000} (85.3%) and CNR_{1000} (86.4%) was greater than those of ADC_{1000} (71.1%; not statistically significant [NS] with a $1 - \beta$ value calculated as a *post hoc* analysis of 0.20 for ADC_{1000} vs RCR_{1000} and $p = 0.034$ for ADC_{1000} vs CNR_{1000}). The AUCs for RCR_{800} (83.5%) and CNR_{800} (83.9%) were greater than those for ADC_{800} (75.7%; NS with a $1 - \beta$ value of 0.06 for both ADC_{800} vs RCR_{800} and ADC_{800} vs CNR_{800}).

When the AUCs of the DW parameters between $b = 1000 \text{ s mm}^{-2}$ and 800 s mm^{-2} were compared for their ability to discriminate pHCC, the RCR_{1000} and CNR_{1000} were shown to be slightly higher than the RCR_{800} and CNR_{800} , whereas the ADC_{1000} was lower than the ADC_{800} (NS for all).

Figure 2. Boxplots of the apparent diffusion coefficient (a, d), relative contrast ratio (b, e) and contrast-to-noise ratio (c, f) sub-grouped into well-differentiated (well), moderately-differentiated (moderate) and poorly-differentiated (poor) hepatocellular carcinoma on $b = 1000 \text{ s mm}^{-2}$ (a–c) and $b = 800 \text{ s mm}^{-2}$ (d–f). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ indicate significant differences. ADC, apparent diffusion coefficient; CNR, contrast-to-noise ratio; RCR, relative contrast ratio.

With respect to differences in DW parameters for each grade between $b = 1000 \text{ s mm}^{-2}$ and 800 s mm^{-2} , the ADC_{1000} for wHCC was found to be significantly lower than the ADC_{800} for wHCC ($p = 0.029$). There were no significant differences in the other parameters.

Differences between institutions

There was no significant difference in ADC, RCR, or CNR for each grade of HCC between the institutions ($p = 0.12$ – 1.00 ; Supplementary file 1, supplementary files available online). The sensitivity and specificity values of the DW parameters for discriminating pHCC were in the ranges of 62.5–100.0% and 33.3–100.0%, respectively, between the institutions; however, there were no significant differences ($p = 0.19$ – 1.00 ; Supplementary file 2).

Interobserver agreement

There was strong agreement for ADC_{1000} [ICC 0.650, 95% CI (0.283–0.820), $p < 0.001$] and almost perfect agreement for RCR_{1000} [ICC 0.926, 95% CI (0.879–0.956), $p < 0.001$] and CNR_{1000} [ICC 0.811, 95% CI (0.700–0.884), $p < 0.001$]. There was strong agreement for ADC_{800} [ICC 0.754, 95% CI (0.355–0.892), $p < 0.001$] and CNR_{800} [ICC 0.628, 95% CI (0.405–0.780), $p < 0.001$], and almost perfect agreement for RCR_{800} [ICC 0.871, 95% CI (0.774–0.929), $p < 0.001$].

Figure 4 shows the results of the Bland–Altman plot for each DW parameter. The mean bias $\pm$ limits of agreement values were $-0.13 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1} \pm 0.353$ for ADC_{1000} , 0.04 ± 1.514 for RCR_{1000} , and 0.48 ± 19.951 for CNR_{1000} , and were $-0.12 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1} \pm 0.316$ for ADC_{800} , 0.16 ± 2.139 for RCR_{800} , and 2.25 ± 27.165 for CNR_{800} .

DISCUSSION

This multivendor study demonstrated that all DW parameters were useful for evaluating the grade of HCC, and that the RCR and CNR tended to be superior to the ADC in predicting the histological grade of HCC, particularly for discriminating pHCCs from other HCCs.

HCC is known to increase T_2 elongation and to restrict diffusion with increasing histological grade.^{18,30,31} The SIs of DWI, which are presented as the RCR and the CNR, are influenced by T_2 elongation as well as restriction of diffusion. Therefore, the RCR and CNR might be more appropriate for predicting the histological grade of HCC than measurement of the ADC alone. Previous studies have shown similar results.^{18,19,21}

ROC analyses revealed that the RCR and CNR on $b = 1000 \text{ s mm}^{-2}$ tended to be superior to the RCR and CNR on $b = 800 \text{ s mm}^{-2}$ for discrimination of pHCCs. Restriction of diffusion is more strongly related to the contrast in DWI on $b = 1000 \text{ s mm}^{-2}$ than on $b = 800 \text{ s mm}^{-2}$ and is considered to be a more important reflection of histological grade. A previous study that used methods similar to those in the present study showed that the AUCs of ADC on $b = 0$ and 1500 s mm^{-2} were greater than those on $b = 800$ – 1000 s mm^{-2} in the present study.¹⁸

However, the AUC of the ADC on $b = 0$ and 1000 s mm^{-2} tended to be inferior to that of the ADC on $b = 0$ and 800 s mm^{-2} in discriminating pHCCs. We speculate that the reason for this was that the ADC_{1000} does not correctly measure restriction of diffusion on wHCC when compared with the ADC_{800} ; the ADC_{1000} on wHCC was shown to be slightly lower than that for mHCC and closer to that for pHCC, whereas the ADC_{800} on wHCC

Table 3. Relationship between histological grade of hepatocellular carcinoma and diffusion-weighted parameters with results of statistical analysis

	$b = 1000 \text{ s mm}^{-2}$			$b = 800 \text{ s mm}^{-2}$		
	ADC ($\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$)	RCR	CNR	ADC ($\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$)	RCR	CNR
wHCC ^a	1.08 ± 0.15	1.76 ± 1.09	9.05 ± 8.86	1.33 ± 0.19	2.22 ± 0.74	13.03 ± 8.54
mHCC ^a	1.19 ± 0.23	2.74 ± 1.45	15.27 ± 11.56	1.20 ± 0.21	2.85 ± 1.83	17.29 ± 12.72
pHCC ^a	1.01 ± 0.19	5.04 ± 2.25	34.54 ± 18.56	1.06 ± 0.39	5.25 ± 3.25	38.22 ± 24.18
Spearman's rank correlation coefficient ^b	-0.27^{b1}	0.62^{b3}	0.64^{b3}	-0.44^{b2}	0.53^{b3}	0.53^{b3}
Kruskal-Wallis test p -value	0.027	<0.001	<0.001	0.017	0.002	0.002
Wilcoxon rank sum test p -value						
wHCC vs mHCC	1.000	0.137	0.706	0.654	0.843	1.000
mHCC vs pHCC	0.031	<0.001	<0.001	0.154	0.015	0.005
wHCC vs pHCC	0.478	<0.001	<0.001	0.019	0.005	0.008
ROC analysis						
wHCC vs mHCC + pHCC cut-off value	1.13	1.83	13.70	1.27	2.18	14.87
AUC ^c	0.504 (0.299, 0.708)	0.820 (0.659, 0.981)	0.760 (0.591, 0.929)	0.720 (0.562, 0.878)	0.728 (0.551, 0.905)	0.703 (0.511, 0.895)
wHCC + mHCC vs pHCC cut-off value	1.13	3.22	17.66	1.10	2.87	16.99
AUC ^c	0.711 (0.569, 0.852)	0.853 (0.757, 0.947)	0.864 (0.773, 0.955)	0.757 (0.552, 0.962)	0.835 (0.705, 0.964)	0.839 (0.712, 0.966)

AUC, area under the curve; ADC, apparent diffusion coefficient; CNR, contrast-to-noise ratio; mHCC, moderately-differentiated hepatocellular carcinoma; pHCC, poorly-differentiated hepatocellular carcinoma; RCR, relative contrast ratio; wHCC, well-differentiated hepatocellular carcinoma.

^aThe data are shown as the mean $\pm$ standard deviation.

^bSignificant differences are indicated as follows: ^{b1} $p < 0.05$, ^{b2} $p < 0.01$, ^{b3} $p < 0.001$.

^cData in parentheses are the 95% confidence intervals.

was highest in all grades. The ADC₁₀₀₀ on wHCC must have the highest values because the RCR and CNR values on wHCC were shown to be lowest for DWI on both $b = 800 \text{ s mm}^{-2}$ and $b = 1000$

s mm^{-2} . This discrepancy can be explained by Rician noise, which increases at a higher b -value and causes a more marked decrease in the ADC on $b = 0$ and 1000 s mm^{-2} than on $b = 0$ and 800 s mm^{-2} .

Figure 3. Receiver operating characteristic curves discriminating poorly-differentiated HCCs from well- and moderately-differentiated HCCs for diffusion-weighted parameters on $b = 1000 \text{ s mm}^{-2}$ (a) and 800 s mm^{-2} (b). The areas under the curve are shown in the boxes. The numbers in parentheses indicate the 95% confidence intervals. ADC, apparent diffusion coefficient; CNR, contrast-to-noise ratio; HCCs, hepatocellular carcinomas; RCR, relative contrast ratio.

Figure 4. Bland-Altman plots of the diffusion weighted parameters between two readers' measurements for the apparent diffusion coefficient (a, d), relative contrast ratio (b, e) and contrast-to-noise ratio (c, f) on $b = 1000 \text{ s mm}^{-2}$ (a–c) and 800 s mm^{-2} (d–f). The central dashed lines indicate the mean absolute difference and the upper and lower lines indicate the 95% limits of agreement. ADC, apparent diffusion coefficient; CNR, contrast-to-noise ratio; RCR, relative contrast ratio.

mm^{-2} for wHCC. However, it is difficult to determine the precise reason for this discrepancy because the ADC could be affected by various factors, *e.g.* the microcapillary perfusion effect.

The previous studies used two main methods to set the ROIs for measuring the ADC values of hepatic tumours. One method was to set the ROIs on the “solid” lesion where the ADC was considered to be the lowest in the entire tumour while avoiding necrotic, haemorrhagic and cystic lesions (known as the “minimum” ADC). The other method was to set the ROIs so that they included the entire lesion (known as the “mean” ADC). To our knowledge, the minimum ADC has consistently been reported to have high diagnostic accuracy for prediction of the histological grade of HCC,^{22,23} whereas studies that have used the mean ADC have yielded inconsistent results.^{17,19,21,26} In the present study, the ROI was set on the solid part of lesion where the SIs seemed to be highest. This method is similar to that used to obtain the minimum ADC and is considered to be appropriate for prediction of HCC grade.

In terms of interobserver variability, the ICCs for the RCR were in almost perfect agreement and were the highest of the DW parameters on each high b -value. The RCR is regarded as clinically useful because of its high diagnostic accuracy and high degree of interobserver reproducibility. The thresholds of RCR for predicting pHCC were approximately “3” at a b -value of 800 and 1000 s mm^{-2} . Moreover, this threshold could be used to predict pHCC at up to 1500 s mm^{-2} , because the threshold was very similar to that in a previous study using a b -value of 1500 s mm^{-2} .¹⁸

Almost all of the previous studies of the relationship between DWI and HCC grade were performed using a single MR unit.^{17–27} Our multivendor study has confirmed and validated the clinical value and relevance of DWI in prediction of HCC grade.

There are several limitations to this study, in particular its retrospective design and small patient population. Further prospective studies in large cohorts are needed. Another limitation is that the reproducibility of RCR and CNR among the different magnetic field strengths and respiratory motion compensation techniques available is unknown. The minimum ADC for hepatic tumours is not significantly different between 1.5 T and 3.0 T,³² and no significant differences in ADC have been identified between the different respiratory motion compensation techniques at 1.5 or 3.0 T.^{33–35} Further assessment of the reproducibility of RCR and CNR using other measurement methods under various conditions of MRI acquisition might be needed. Finally, some of the HCCs were located in the subdiaphragmatic area, where image quality is known to deteriorate because of cardiac motion artefacts.

In conclusion, this multivendor study demonstrated that RCR, CNR and ADC with a b -value of 800 and 1000 s mm^{-2} could discriminate HCC grade, and that DW parameters were able to distinguish well- and moderately-differentiated HCC from poorly-differentiated HCC with non-ADC parameters being more useful than ADC itself. A RCR threshold of more than 3 might predict pHCC with higher interobserver reproducibility.

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