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Pre-operative ADC predicts early recurrence of HCC after curative resection

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Abstract

Objectives To assess a correlation between the preoperative diffusion-weighted imaging (DWI) and early recurrence (<2 years) and to determine the best DWI parameters as the risk factor of early recurrence after surgery in single hepatocellular carcinoma (HCC).

Methods The study included 114 patients with surgically resected single HCC (≤5 cm) who underwent preoperative magnetic resonance imaging (MRI) with DWI. Radiologists evaluated the diffusion restriction of the tumours using qualitative assessment and the mean and minimum apparent diffusion coefficient values (ADCmean and ADCmin) of the tumours using quantitative measurement. Clinical and laboratory findings and DWI parameters as a risk factor for early recurrence were identified by using Cox proportional hazards model.

Results No significant difference was observed in early recurrence rates of HCCs between those with and those without diffusion restriction ($p = 0.484$). Early recurrence rates of HCCs with ADCmean and ADCmin values lower than the optimal cut-offs (1.023 and 0.773×10^{-3} mm^2/s, respectively) were significantly higher compared with those with values higher than the optimal cut-offs ($p = 0.001$ and $p < 0.001$, respectively). In the multivariable analysis, tumour size [hazard ratio (HR) per centimetre, 2.011; 95% CI, 1.304-3.102; $p = 0.002$] and ADCmin ≤0.773×10^{-3} mm^2/s (HR, 13.339; 95% CI, 4.422-40.240; $p < 0.001$) were independent risk factors for early HCC recurrence.

Conclusions DWI is a promising imaging tool for early recurrence of HCC. Among qualitative and quantitative assessments of DWI, ADCmin is a significant risk factor for early recurrence after surgery in single HCC.

Key Points

- *The performance of minimum apparent diffusion coefficient (ADCmin) is significantly better than that of mean apparent diffusion coefficient (ADCmean) for identifying early recurrence.*
- *ADCmin is a significantly independent risk factor of early HCC recurrence after surgery.*
- *ADCmin correlates with early recurrence after curative resection of single HCC, reflecting histopathological features of the tumours including histological grade and microvascular invasion.*

Keywords Hepatocellular carcinoma · Magnetic resonance imaging · Diffusion-weighted imaging · Early recurrence

Abbreviations

AFP	Alpha-fetoprotein
HBP	Hepatobiliary phase
HCC	Hepatocellular carcinoma
HR	Hazard ratio
MVI	Microvascular invasion
PIVKA-II	Protein induced by vitamin K absence or antagonist-II

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Introduction

Diffusion-weighted imaging (DWI) is a complementary magnetic resonance imaging (MRI) technique that reflects tumour cellularity, which can be used to characterise benign and malignant liver lesions [1–3]. Especially, DWI has improved both the diagnostic accuracy and specificity of hepatocellular carcinoma (HCC) and restricted diffusion were incorporated to the Liver Imaging Reporting and Data System (LI-RADS) as ancillary features favouring malignancy [4, 5]. Furthermore, recent studies have suggested that DWI may be used for predicting histologic differentiation [6–11] and microvascular invasion (MVI) [11–13] of hepatocellular carcinoma (HCC). However, results [6–13] have varied depending on the definition of restricted diffusion and the DWI measurement method.

According to the recent clinical practice guideline of HCC, the cut-off of 2 years has been adopted to classify early and late recurrences [14, 15]. Risk factors of early recurrence within the first 2 years after surgical resection in HCC have been studied. It has been reported that tumour factors such as poor histological differentiation, MVI, and high serum alpha-fetoprotein (AFP) are have been associated with early recurrence after tumour resection [16–19]. The relationship between DWI and postoperative pathological examination such as histologic grade and MVI implies that DWI could be used as a risk factor for early recurrence. DWI provides information about the degree of diffusion restriction by qualitative visual assessment, as well as by quantitative measurements of the apparent diffusion coefficient (ADC) values [3, 20]. Among quantitative measurements of ADC values, mean ADC value (ADCmean) calculated from region of interest (ROI) of the tumour is commonly used [20]. Meanwhile, several studies have adopted the minimum ADC value (ADCmin) in the ROI and have reported a significant correlation between ADCmin and histological grade in HCC [8, 10].

A previous study by Nakanishi et al [10] has reported that ADCmin was a significant risk factor for early recurrence within 6 months after surgery. In the study, however, qualitative parameter of DWI such as diffusion restriction was not analysed as a risk factor of early recurrence and patients with multiple HCCs and large tumours (up to 15 cm) were enrolled. To the best of our knowledge, among qualitative (presence or absence of diffusion restriction) and quantitative (ADCmean and ADCmin) methods, the best DWI parameter as a risk factor for early recurrence (<2 years) after curative resection in patients with early-stage single HCC has not been established yet.

The purpose of our study was to assess a correlation between the preoperative DWI and early recurrence (<2 years) and to determine the best DWI parameter as a risk factor of early recurrence after curative resection in single HCC (≤5 cm).

Materials and methods

Study population

This retrospective study was approved by the institutional review board, and the requirement for informed consent was waived.

Between January 2013 and December 2013, 247 consecutive patients underwent curative hepatic resection for single HCC ≤5 cm. Of these, 176 patients underwent preoperative MRI including DWI at our institution within 1 month before surgery. Patients were excluded from the study if they had a previous treatment history of HCC including transcatheter arterial chemoembolisation (n = 43), radiofrequency ablation (n = 7), and hepatectomy (n = 6), or if they had DWI inadequate for analysis (n = 6). DWI inadequate for analysis consisted of HCCs which were located at the subdiaphragmatic region and left lateral section of the liver. The evaluation of these lesions may be inaccurate because of the considerable imaging deterioration due to cardiac motion-related artefacts [3].

Finally, 114 patients (mean age, 58.0 years; range, 33-78 years), comprising 90 men (mean age, 56.7 years; range, 33-78 years) and 24 women (mean age, 62.7 years; range, 43-73), were included in this study. The background liver was normal in three patients, whereas 58 patients had chronic hepatitis and 53 had cirrhosis. The aetiology of liver disease was viral hepatitis type B in 101 patients, type C in five and other origins in eight. The types of surgical resection were wedge resection in 15 patients, segmentectomy in 34, left lateral sectionectomy in nine, right anterior sectionectomy in six, right posterior sectionectomy in eight, central hepatectomy in six, and hemihepatectomy in 36. The mean interval between MR examination and surgery was 13 days (range, 6-30 days).

MRI protocol

All examinations were performed using a 3.0-T whole-body MRI system (Intera Achieva 3T; Philips Healthcare, Andover, MA, USA) equipped with a dual-source parallel radiofrequency transmission system and a quadrature body coil. DWI was performed by using a respiratory-triggered single-shot echo planar imaging with b values of 0, 100, and 800 s/mm^2. A spectral attenuated inversion-recovery technique was used for fat suppression on DWI. The scanning parameters were as follows: repetition time/echo time, 1,600/70 ms; flip angle, 90°; matrix size, 112 × 108; bandwidth, 79.5 Hz/pixel; section thickness, 5 mm; number of excitations, 4; field of view of 32-38 cm. ADC was calculated using a monoexponential function with b values of 0 and 800 s/mm^2.

For gadoxetic acid (Primovist; Bayer Healthcare, Leverkusen, Germany)–enhanced MR imaging, unenhanced, enhanced arterial phase (20–35 s), portal venous phase (60 s), delayed phase (3 min) and 20-min hepatobiliary phase (HBP) images were obtained using a

T1-weighted three-dimensional (3D) turbo-field-echo sequence (T1 high-resolution isotropic volume examination, THRIVE; Philips Healthcare). The timing for arterial phase imaging was determined using a MR fluoroscopic bolus detection technique. The contrast agent was automatically administered intravenously using a power injector at a rate of 2 mL/s for a total dose of 0.025 mmol/kg body weight, followed by a 20-mL saline flush.

Imaging analysis

Two abdominal radiologists (S.L. and S.H.K., with 6 and 17 years of experience, respectively, in liver MRI) independently reviewed all images on a commercial workstation equipped with a 2,000 × 2,000 Picture Archiving and Communication System (PACS, Centricity 3.0; GE Healthcare, Chicago, IL, USA) monitor with the ability to adjust the optimal window setting for each case. They were blinded to clinical, laboratory, histopathological and follow-up results, but were aware that the study population consisted of HCC.

T2-weighted and DWI with ADC map were assessed side-by-side using a spatial cursor key function that assisted in matching corresponding sites on different images via multiplanar localisation. For qualitative assessment, the radiologists visually assessed the signal intensity (SI) of HCC on DWI and determined the presence or absence of diffusion restriction at the level of the maximum diameter of the tumour. In this study, diffusion restriction was defined as the presence of hyperintensity on DWI with a high *b* value (b = 800 s/mm^2) and isointensity or hypointensity on the ADC map, compared with the SI of the background liver. [21] After independent image review, interobserver agreement was evaluated and discordant results between the radiologists were adjusted by consensus. For quantitative assessment, the radiologists independently measured ADC values. ROIs were placed at the level of the maximum diameter of the lesion and were manually traced on lesion borders to include the largest tumour area. Necrotic or haemorrhagic areas or artefacts were avoided by referring to T2-weighted images and contrast-enhanced T1-weighted images. ADC values were assessed using two methods: ADCmean and ADCmin [10]. By drawing ROI on the ADC maps, ADCmean and ADCmin were automatically displayed on a workstation. Mean ROI size was 310.1 mm^2 (range, 26.1-1,490.9 mm^2). ADCmean was defined as the average ADC value in the ROI and ADCmin was defined as the lowest ADC value in the ROI. For each ADCmean and ADCmin value, the average of the measurement by the two radiologists was used for analysis.

Tumour size, which was defined as the maximum diameter on axial images, was measured on HBP images by a third radiologist (J.A.H., with 7 years of experience in liver MRI).

Histopathological evaluation

Histopathological factors were assessed for each tumour by one hepatic pathologist, including histologic grade and microvascular invasion. Histological grade was classified as well differentiated, moderately differentiated or poorly differentiated according to the Edmonson-Steiner nuclear grading system [22]. When different histological grades coexisted within a tumour, the predominant grade was used as the tumour grade. MVI was defined as a tumour within a vascular space lined by endothelium that was visible only on microscopy.

Follow-up after surgical resection

For follow-up after curative resection of HCC, patients underwent physical examination, chest radiography, and laboratory tests including liver function tests, AFP and PIVKA-II, 1 month after surgery and every 2-3 months thereafter. Multiphasic computed tomography (CT) was performed every 3 months or when recurrence was suspected. Gadoxetic acid–enhanced MRI and/or positron emission tomography scans were obtained when CT could not provide obvious evidence of a suspected recurrence. Early recurrence was defined as intrahepatic and/or extrahepatic recurrence of HCC within 2 years after curative resection.

Statistical analysis

To compare preoperative characteristics between HCCs with or without early recurrence, we used the χ^2 test or Fisher exact test for categorical variables and the two-sample *t*-test or Mann-Whitney *U* test for continuous variables.

Interobserver agreement for qualitative (visual) interpretation of diffusion restriction was verified using the Cohen κ statistic. The κ value (the level of agreement) was defined as follows: κ < 0.21, poor; κ = 0.21–0.40, fair; κ = 0.41–0.60, moderate; κ = 0.61–0.80, good; κ > 0.80, excellent agreement. Pearson's correlation test was used to test the correlation between the quantitative measurements of ADC values. The correlation coefficients (*r*) from these comparisons were used.

Receiver operating characteristic (ROC) curves of ADCmean and ADCmin values were generated to calculate the optimal cut-off values with adequate sensitivity and specificity to predict early recurrence, and then compared.

Early recurrence rates were estimated by the Kaplan-Meier method and the log-rank test was used to compare patient groups. Univariable and multivariable analyses for predicting early recurrence were performed using a Cox proportional hazards model. Variables with *p* values of <0.05 in the univariable analysis were chosen as variables for the multivariable analysis. For the multivariable analysis, a stepwise backward elimination method was used.

Differences in ADC values according to histological grade were analysed using one-way analysis of variance. Tukey test was applied for multiple comparisons. The relationship between ADC values of HCCs and MVI were compared using the two-sample *t*-test.

SPSS version 21.0 (IBM, Armonk, New York, USA) and MedCalc version 16.2.1 (MedCalc Software, Ostend, Belgium) were used for the statistical analyses. A p value of <0.05 was considered statistically significant.

Results

Comparisons of preoperative characteristics between HCCs with or without early recurrence

Twenty-five (21.9%) of 114 patients with single HCC had early recurrence. Twenty-two (88.0%) patients had intrahepatic recurrence and three (12.0%) had extrahepatic recurrence (two patients with lung metastasis and one with lymph node metastasis). Of these 25 patients with early HCC recurrence, the background liver was chronic hepatitis in 12 patients and cirrhosis in 13 patients. Comparisons of preoperative characteristics between HCCs with or without early recurrence are summarised in Table 1. Baseline variables, including age, sex, aetiology of liver disease, presence of liver cirrhosis, Child-Pugh score, Model for End Stage Liver Disease (MELD) score and tumour markers were not statistically significantly different between the groups ($p > 0.05$). Tumour size of HCCs with early recurrence was significantly larger than that of HCCs without early recurrence ($p = 0.020$). Among the DWI parameters, visually accessed diffusion restriction was not significantly different between HCCs with or without early recurrence (Figs. 1 and 2). In contrast, the mean values of ADCmean and ADCmin of HCCs with early recurrence were significantly lower than those of HCCs without early recurrence ($p = 0.002$ and $p < 0.001$, respectively).

Interobserver agreement and correlation for DWI parameters

Interobserver agreement for the presence or absence of diffusion restriction was good ($\kappa = 0.696$, 95% confidence interval (CI) 0.511-0.882, $p < 0.001$). There was a significant positive correlation between interobservers for the quantitative measurements of ADCmean and ADCmin ($r = 0.715$; $p < 0.001$ and $r = 0.871$; $p < 0.001$).

Comparison of early recurrence between groups according to DWI parameters

The optimal cut-off values of ADCmean and ADCmin determined by ROC analysis for identifying early recurrence were $\leq 1.023 \times 10^{-3}$ mm^2/s and $\leq 0.773 \times 10^{-3}$ mm^2/s, respectively. With these cut-off values, ADCmean showed a sensitivity of 72.0% and a specificity of 62.9% in identifying early recurrence, whereas ADCmin provided a sensitivity of 84.0% and a specificity of 71.9%. The area under the receiver operating characteristic curve of ADCmin (0.808; 95% CI, 0.724-0.876) was significantly greater than that of ADCmean (0.698; 95% CI, 0.605-0.781) ($p = 0.022$) (Fig. 3).

There was no significant difference in early recurrence rates of HCCs between groups qualitatively categorised by the presence or absence of diffusion restriction (22.9% vs 16.7% in 2 years, $p = 0.484$, Fig. 4a), whereas early recurrence rates of HCCs with ADCmean $\leq 1.023 \times 10^{-3}$ mm^2/s and ADCmin $\leq 0.773 \times 10^{-3}$ mm^2/s were significantly higher compared with those with ADCmean $> 1.023 \times 10^{-3}$ mm^2/s and ADCmin $> 0.773 \times 10^{-3}$ mm^2/s (35.3% vs 11.1% in 2 years, $p = 0.001$, Fig. 4b and 45.7% vs 5.9% in 2 years, $p < 0.001$, Fig. 4c).

Preoperative risk factors of early recurrence

The results of Cox proportional hazards regression to identify factors associated with early recurrence of HCC are presented in Table 2. According to the multivariable analysis, tumour size [hazard ratio (HR) per centimetre, 2.011; 95% CI, 1.304-3.102; $p = 0.002$] and ADCmin $\leq 0.773 \times 10^{-3}$ mm^2/s (HR, 13.339; 95% CI; 4.422-40.240; $p < 0.001$) were significantly independent risk factors for early recurrence after surgery.

Relationship between DWI parameters, and histological differentiation and MVI

There was no relationship between visually assessed diffusion restriction and histological grade of HCCs (well differentiated, 14/17, 82.4%; moderately differentiated, 75/89, 84.3%; and poorly differentiated, 7/8, 87.5%; $p = 0.947$). When ADC values were compared by histological grade, there was no statistical difference between the mean values of ADCmean of different histological groups [$p = 0.767$ for well-differentiated ($1.119 \pm 0.233 \times 10^{-3}$ mm^2/s) vs moderately differentiated ($1.081 \pm 0.202 \times 10^{-3}$ mm^2/s), $p = 0.125$ for well-differentiated vs poorly differentiated ($0.947 \pm 0.131 \times 10^{-3}$ mm^2/s), and $p = 0.179$ for moderately differentiated vs poorly differentiated HCCs] (Fig. 5a). In contrast, the mean values of ADCmin were significantly lower for poorly differentiated HCCs ($0.642 \pm 0.240 \times 10^{-3}$ mm^2/s) than they were for well differentiated ($0.865 \pm 0.198 \times 10^{-3}$ mm^2/s, $p = 0.028$) or for moderately differentiated HCCs ($0.837 \pm 0.197 \times 10^{-3}$ mm^2/s, $p = 0.026$) (Fig. 5b).

Visually assessed diffusion restriction was significantly more frequent in HCCs with MVI than in those without MVI (35/37, 94.6% vs 61/77, 79.2%, $p = 0.035$). The mean values of ADCmean ($0.968 \pm 0.150 \times 10^{-3}$ mm^2/s) and

Table 1 Comparison of preoperative patient characteristics according to early recurrence

Variables	All patients (n = 114)	No early recurrence (n = 89)	Early recurrence (n = 25)	p value
Age (years)[a]	58.0 ± 9.7	58.6 ± 9.5	55.9 ± 10.0	0.221
Sex				0.483
Men	90 (78.9)	69 (77.5)	21 (84.0)	
Women	24 (21.1)	20 (22.5)	4 (16.0)	
Aetiology of liver disease				0.504
Hepatitis B	101 (88.6)	79 (88.8)	22 (88.0)	
Hepatitis C	5 (4.4)	3 (3.4)	2 (8.0)	
Other	8 (7.0)	7 (7.9)	1 (4.0)	
Liver cirrhosis				0.125
No	61 (53.5)	51 (57.3)	10 (40.0)	
Yes	53 (46.5)	38 (42.7)	15 (60.0)	
Child-Pugh score[b]	6 (5-6)	6 (5-6)	6 (5-7)	0.675
MELD score[b]	9 (7-12)	8 (7-11)	9 (7-12)	0.450
AFP (ng/mL)[b]	8.6 (3.7-119.4)	6.7 (3.2-120.0)	15.1 (5.0-105.8)	0.187
PIVKA-II (mAU/mL)[b]	32 (21-74)	31 (20-62)	59 (24-252)	0.068
Tumour size (cm)[b]	2.5 (2.0-3.1)	2.3 (1.9-3.0)	2.8 (2.4-3.5)	0.020
Diffusion restriction				0.556
Absence	18 (15.8)	15 (16.9)	3 (12.0)	
Presence	96 (84.2)	74 (83.1)	22 (88.0)	
ADCmean (× 10^{-3} mm^2/s)[a]	1.078 ± 0.205	1.111 ± 0.207	0.969 ± 0.160	0.002
ADCmin (× 10^{-3} mm^2/s)[a]	0.827 ± 0.205	0.808 ± 0.171	0.640 ± 0.210	<0.001

Unless indicated otherwise, data represent the number of patients, with percentages *in parentheses*

Categorical variables were compared by using the $\chi 2$ test or Fisher exact test

MELD Model for End-Stage Liver Disease, *AFP* alpha-fetoprotein, *PIVKA-II* protein induced by vitamin K absence or antagonist-II,

ADCmean mean apparent diffusion coefficient, *ADCmin* minimum apparent diffusion coefficient

[a] Data are means ± standard deviations and compared by using the two-sample *t*-test

[b] Data are medians, with interquartile ranges in parentheses and compared by using the Mann-Whitney *U* test

ADCmin (0.687 ± 0.199 × 10^{-3} mm^2/s) of HCCs with MVI were significantly lower than those with no MVI (1.130 ± 0.208 × 10^{-3} mm^2/s, $p < 0.001$, Fig. 6a and 0.895 ± 0.172 × 10^{-3} mm^2/s, $p < 0.001$, Fig. 6b).

Discussion

Our study showed that among qualitative parameters (as assessed using visual inspection of the presence or absence of diffusion restriction) and quantitative parameters (as assessed using ADCmean and ADCmin), ADCmin was a relatively more reliable factor for correlating early recurrence (<2 years) after curative resection of single HCC and reflected histological grade of HCC. The optimal cut-off values of ADCmean and ADCmin for identifying early recurrence were ≤1.023 and ≤0.773 × 10^{-3} mm^2/s, respectively. The performance of ADCmin for identifying early recurrence was significantly better than that of ADCmean. Furthermore, among the DWI parameters, ADCmin was the only significantly independent risk factor for early recurrence.

As histological grade of HCC increases, cellular atypia in viable tumours such as mitotic activity and nucleus/cytoplasm ratio increase [22]. This would theoretically decrease free diffusion of water molecules in the intracellular space and lead to a reduced ADC value [20], whereas microscopic or macroscopic tumour necrosis results in an increase in the ADC value [23–25]. These tumour characteristics may thus affect the observed ADC value in HCC. Several studies have evaluated the relationship between DWI and histological grade of HCC and reported that in qualitative analysis using SI on high *b* value (*b* = 800 or 1,000 s/mm^2) DWI, visually assessed SI of HCCs tended to increase as histological grade increased [6, 9, 26]. In addition, several studies have evaluated the relationship between quantitative ADC values (ADCmean or ADCmin) and histological grade of HCCs [6–8, 10, 26]. In prior studies,

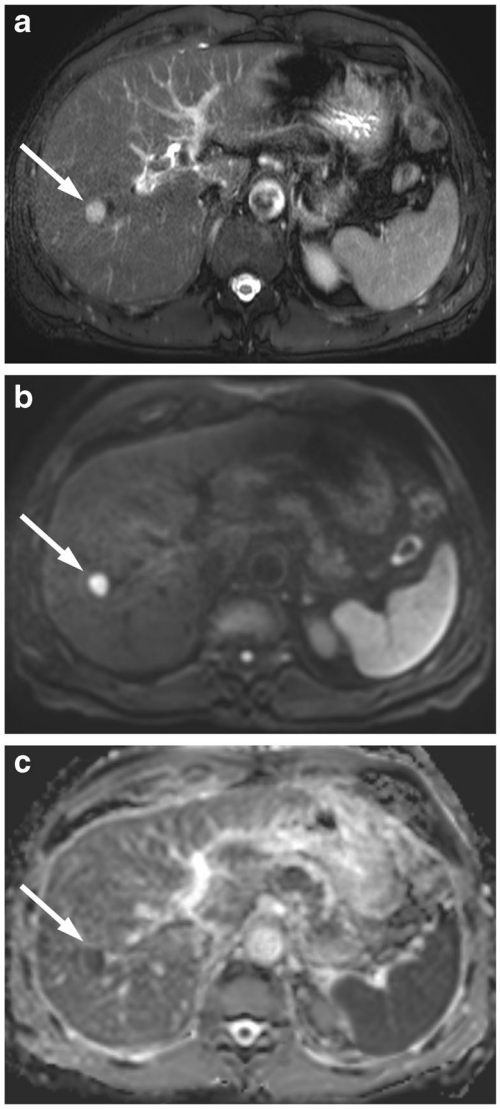

Fig. 1 Images from a 60-year-old man with a 1.5-cm single hepatocellular carcinoma (HCC). **a** Axial respiratory-triggered single-shot T2-weighted magnetic resonance imaging (MRI) shows a hyperintense mass (*arrow*) in the right liver. **b** Axial single-shot echo-planar diffusion-weighted imaging (DWI) (b = 800 s/mm^2) and **c** an apparent diffusion coefficient (ADC) map show a tumour (*arrow*) with visually assessed diffusion restriction. On quantitative assessment, mean ADC (ADCmean) and minimum ADC (ADCmin) of the tumour were 0.840 × 10^{-3} mm^2/s below the optimal cut-off (1.023 × 10^{-3} mm^2/s) of ADCmean and 0.793 × 10^{-3} mm^2/s above the optimal cut-off (0.773 × 10^{-3} mm^2/s) of ADCmin, respectively. On histopathology after surgery, the tumour was classified as well differentiated HCC without microvascular invasion. Tumour recurrence did not occur during 43 months of follow-up period after curative resection

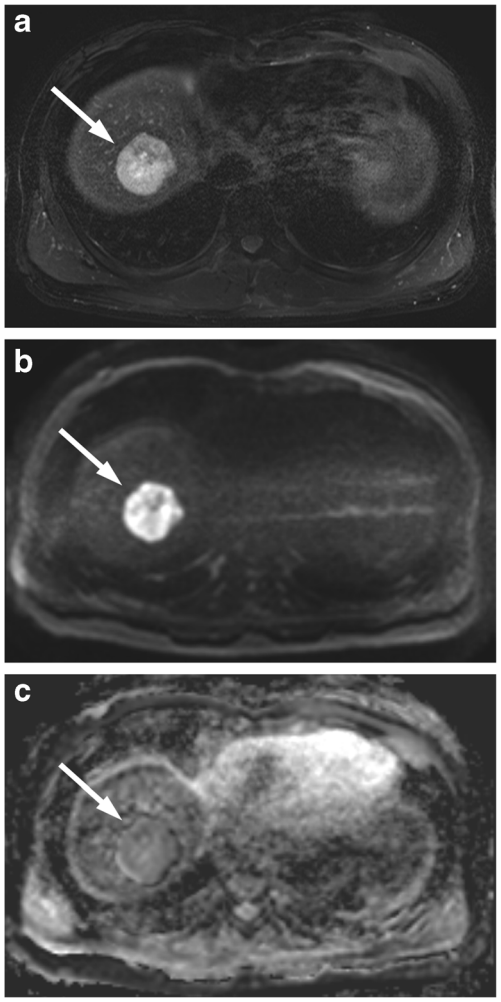

Fig. 2 Images from a 53-year-old man with a 4.6-cm single HCC. **a** Axial breath-hold multi-shot T2-weighted MRI shows a heterogeneously hyperintense mass (*arrow*) in the right liver. **b** Axial single-shot echo-planar DWI (b = 800 s/mm^2) and **c** an ADC map show a tumour (*arrow*) with no visually assess diffusion restriction. On quantitative assessment, mean ADC (ADCmean) and minimum ADC (ADCmin) of the tumour were 1.240 × 10^{-3} mm^2/s above the optimal cut-off (1.023 × 10^{-3} mm^2/s) of ADCmean and 0.737 × 10^{-3} mm^2/s below the optimal cut-off (0.773 × 10^{-3} mm^2/s) of ADCmin, respectively. On histopathology after surgery, the tumour was classified as poorly differentiated HCC with microvascular invasion. Tumour recurrence occurred in the liver four months after curative resection

there is, however, a lack of consensus regarding the relationship between ADCmean and histologic grades of HCCs. Muhi et al [6] reported that the ADCmean values of moderately to poorly differentiated HCCs were significantly lower than those of well differentiated HCCs. Heo et al [7] demonstrated that the ADCmean of poorly differentiated HCCs was lower than that of well differentiated and moderately differentiated HCCs, whereas Nasu et al [26] showed that the ADCmean of HCCs had no correlation with histologic grade. On the other hand, studies using ADCmin have reported that ADCmin predicts histologic grade of HCCs. Nishie et al [8] and Nakanishi et al [10] have reported that the ADCmin of poorly differentiated HCCs was significantly lower than that of well or moderately differentiated HCCs. In our study, visually assessed diffusion restriction and ADCmean had no correlation with histologic grade of HCCs, whereas the mean value of ADCmin of poorly differentiated HCCs was significantly lower than that of well and moderately differentiated HCCs. We think that ADCmin might better reflect histological grade

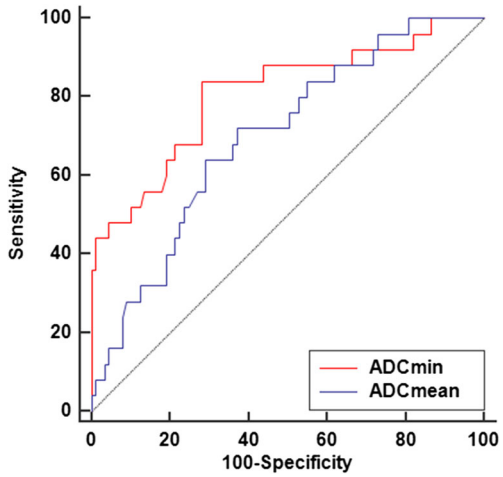

Fig. 3 Receiver operating characteristic curves of ADCmean and ADCmin for predicting early recurrence of HCC

of the viable solid portion of HCCs because it minimises the effect of microscopic or macroscopic necrosis within the tumour and corresponds with the highest tumour cellularity [13]. Although visible necrotic areas of HCC were excluded when drawing the ROIs, we think that invisible microscopic necrosis might not be excluded. Therefore, we speculate that ADCmean may reflect the ADC values of microscopic necrotic portion as well as viable solid portion of HCCs.

A prior study showed that DWI using $b = 50$, 400 and 800 s/mm^2 could be applied to the preoperative assessment of MVI in HCC [12]. The study demonstrated that HCCs with MVI had higher lesion-to-liver SI ratios on DWI for each b value and lower ADCmean compared with those without MVI [12]. Another study reported that HCCs with MVI had lower ADCmean and lower ADCmin than did HCCs without MVI [13]. In our study, visually assessed diffusion restriction

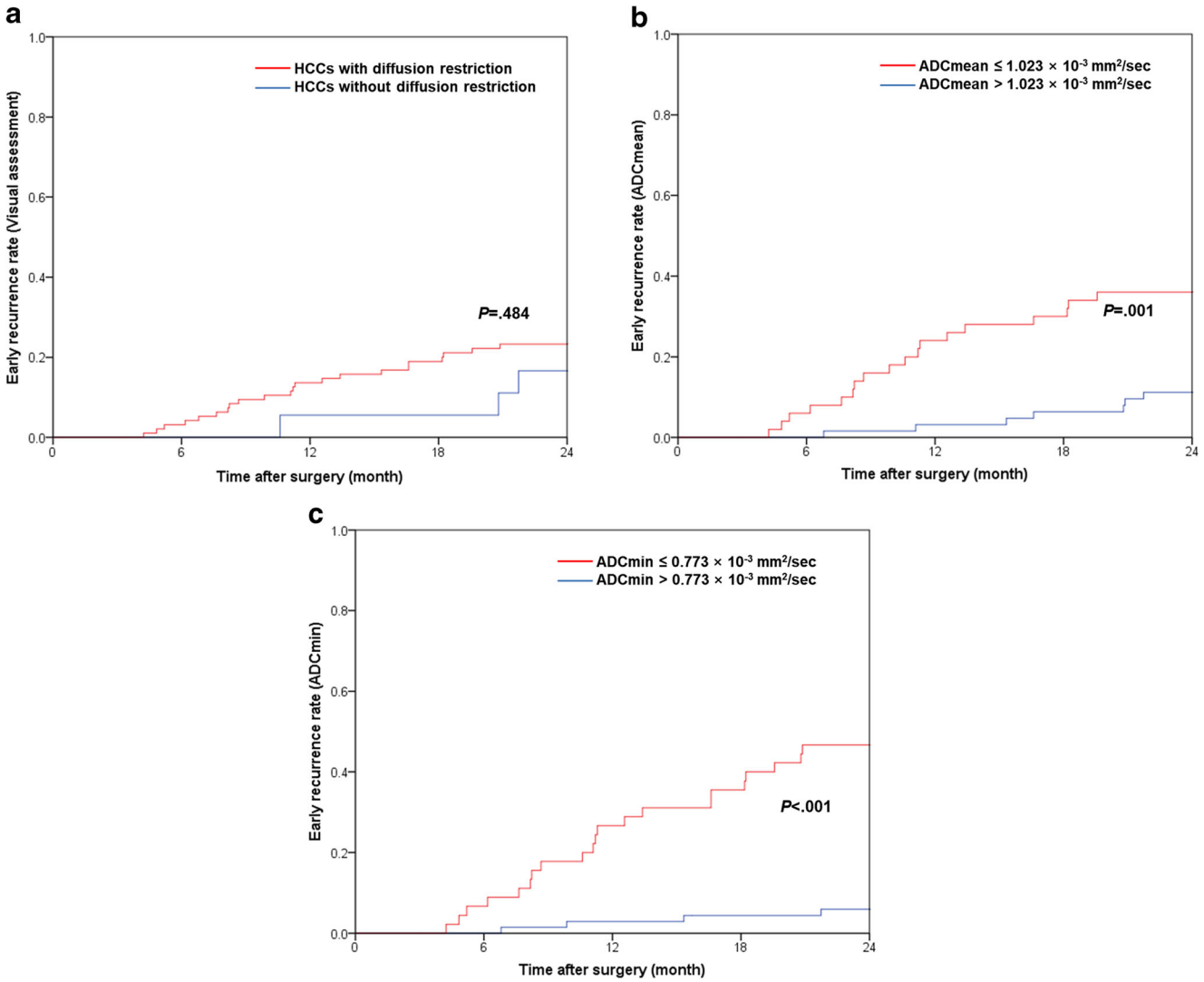

Fig. 4 Kaplan-Meier curves for cumulative early recurrence rate of HCC patients (**a**) with or without diffusion restriction, (**b**) with ADCmean ≤1.023 × 10^{-3} mm^2/s or >1.023 × 10^{-3} mm^2/s and (**c**) with ADCmin value ≤0.773 × 10^{-3} mm^2/s or >0.773 × 10^{-3} mm^2/s. Statistical significance was assessed with the log-rank test

Table 2 Cox proportional hazard analysis of early recurrence of HCC with preoperative variables

Parameter	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (years)	0.973 (0.935-1.014)	0.192		
Sex				
Male	1	–		
Female	0.692 (0.238-2.017)	0.500		
Aetiology of liver disease				
Hepatitis B	1	–		
Hepatitis C	1.855 (0.436-7.894)	0.403		
Other	0.518 (0.707-3.841)	0.520		
Liver cirrhosis				
No	1	–		
Yes	1.896 (0.852-4.221)	0.117		
Child-Pugh score	1.179 (0.781-1.779)	0.434		
MELD score	1.072 (0.962-1.194)	0.210		
AFP (ng/mL)	1.000 (1.000-1.000)	0.695		
PIVKA-II (mAU/mL)	1.001 (0.999-1.002)	0.001 [a]		
Tumour size (cm)	1.537 (1.045-2.262)	0.029 [a]	2.011 (1.304-3.102)	0.002 [a]
Diffusion restriction				
Absence	1	–		
Presence	1.534 (0.459-5.125)	0.487		
ADCmean ($\times 10^{-3}$ mm^2/s)				
>1.023	1	–		
≤1.023	3.943 (1.645-9.451)	0.002[a]		
ADCmin ($\times 10^{-3}$ mm^2/s)				
>0.773	1	–	1	–
≤0.773	10.211 (3.498-29.803)	<0.001[a]	13.339 (4.422-40.240)	<0.001[a]

was significantly more frequent in HCCs with MVI than in those without MVI. Also, the mean values of ADCmean and ADCmin of HCCs with MVI were significantly lower than those of HCCs without MVI, which is consistent with previous studies [12, 13].

Hepatic resection has been one of the most effective treatments for HCC, but the high incidence of tumour recurrence remains a challenge. Intrahepatic HCC recurrence within 2 years after surgical resection is usually classified as early recurrence and that occurring beyond 2 years after surgery is characterised as late recurrence [14, 15, 17, 18]. Early recurrence is considered as originating from the initial tumour, whereas late recurrence is thought to result from de novo multicentric occurrence in underlying cirrhotic liver [14–17, 27]. Recent studies have shown that early recurrence is affected by adverse tumour features such as worse histological differentiation and MVI [16–19]. A prior study suggested that DWI before surgical resection could predict early recurrence [10]. Nakanishi et al [10] reported that the values of ADCmin but not of ADCmean were significantly lower in patients with early recurrence compared with that of patients without early recurrence and ADCmin but not ADCmean was an independent risk factor for "early recurrence <6 months". In this study [10], however, qualitative assessment of DWI such as diffusion restriction was not analysed as a risk factor of early recurrence and patients with multiple and large tumours (up to 15 cm) were enrolled. In our study with only early-stage HCCs (≤5 cm), among qualitative and quantitative DWI parameters, ADCmin was the only significantly independent risk factor for "early recurrence <2 years" after curative resection. Based on this result, we think that ADCmin might better reflect aggressive histological features which affect early recurrence, such as worse histological grade and MVI.

Preoperative estimation of aggressive histological features of HCC non-invasively based on imaging findings is very important for reducing early recurrence after surgical resection. We think that lower ADCmin of HCC may help surgeons decide appropriate surgical procedures (i.e. a wide resection margin) before surgery. Furthermore, patients with HCC of low ADCmin may require intensive follow up after surgery. Earlier identification and treatment of early recurrence by intensive follow-up may improve the survival of patients.

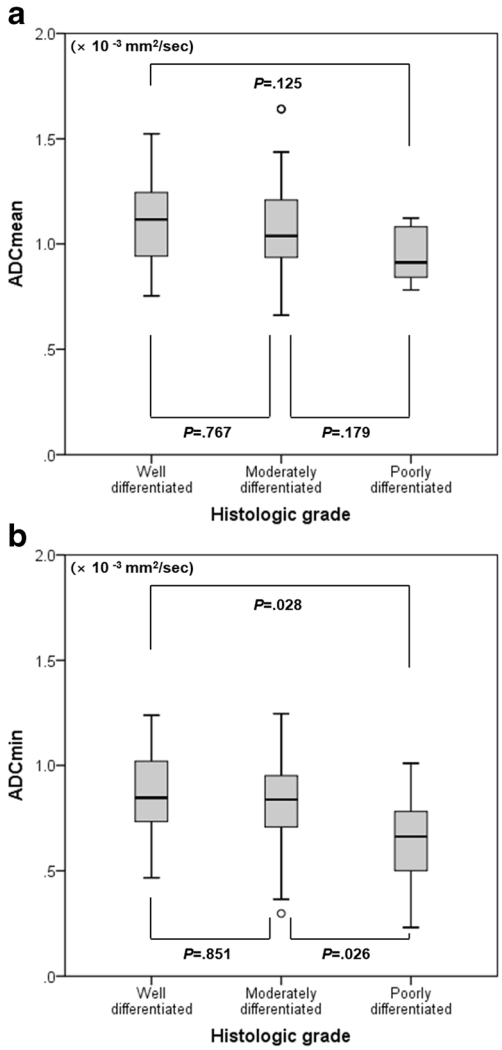

Fig. 5 Box plots between ADC values and histologic grade of HCCs, according to (**a**) ADCmean and (**b**) ADCmin. Differences in ADC values according to histological grade were analysed using one-way analysis of variance. Tukey test was applied for multiple comparisons

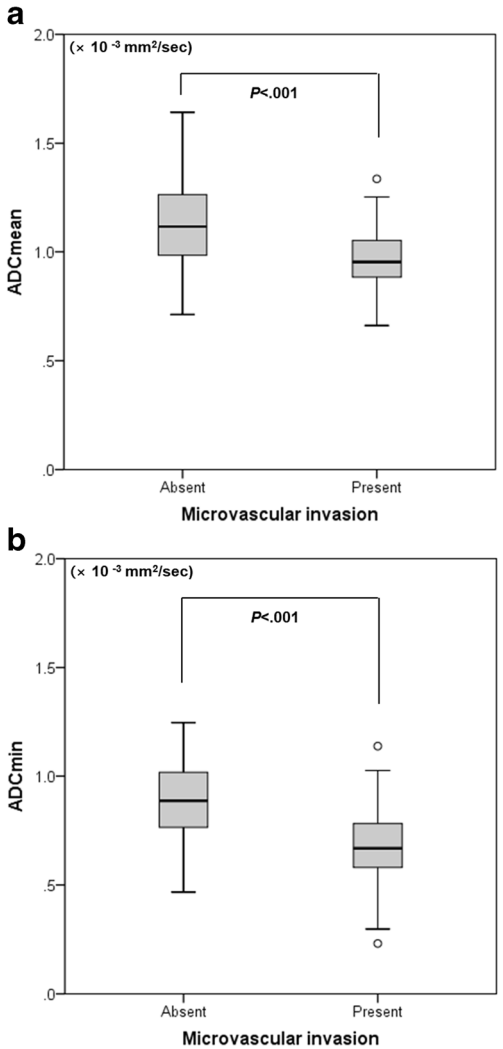

Fig. 6 Box plots between ADC values and microvascular invasion of HCCs, according to (**a**) ADCmean and (**b**) ADCmin. The relationship between ADC values of HCCs and microvascular invasion were compared using the two-sample *t*-test

Our study had some limitations. First, it is prone to potential selection bias due to the retrospective nature of this study. Second, ADC values were calculated at the level of the maximum diameter of the lesion instead of the whole tumour region, which may not have fully represented histopathologic heterogeneity of the tumour. Third, tumour size was confined to ≤5 cm in our study; therefore, the results cannot be generalised to HCC larger than 5 cm in diameter. Fourth, the identified cut-off values of ADC in our study were not tested in a separate test cohort to verify the optimal cut-off values. Fifth, we did not evaluate maximum ADC value (ADCmax) as preoperative DWI parameter of HCCs, which might more reflect necrotic area rather than solid viable portion of HCC. Lastly, our results were from a single-centre study in an endemic area for hepatitis B virus infection; thus, they might not be applicable to other population with different aetiologies of liver disease. Further prospective confirmation of the results in a multicentre setting that includes a larger number of patients with various aetiologies of liver disease would be needed.

In conclusion, DWI is a promising imaging tool for early recurrence of HCC. Among qualitative and quantitative assessments of DWI, ADCmin of HCC is a significant risk factor for early recurrence after surgery in single HCC.

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Statistics and biometry One of the authors has significant statistical expertise.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- retrospective
- prognostic study
- performed at one institution

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