

Histogram analysis of apparent diffusion coefficient predicts response to radiofrequency ablation in hepatocellular carcinoma

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Abstract

Objective: The aim of this study was to predict tumor progression in patients with hepatocellular carcinoma (HCC) treated with radiofrequency ablation (RFA) using histogram analysis of apparent diffusion coefficients (ADC).

Methods: Breath-hold diffusion weighted imaging (DWI) was performed in 64 patients (33 progressive and 31 stable) with biopsy-proven HCC prior to RFA. All patients had pre-treatment magnetic resonance imaging (MRI) and follow-up computed tomography (CT) or MRI. The ADC values (ADC_{10} , ADC_{30} , ADC_{median} and ADC_{max}) were obtained from the histogram's 10th, 30th, 50th and 100th percentiles. The ratios of ADC_{10} , ADC_{30} , ADC_{median} and ADC_{max} to the mean non-lesion area-ADC ($RADC_{10}$, $RADC_{30}$, $RADC_{median}$, and $RADC_{max}$) were calculated. The two patient groups were compared. Key predictive factors for survival were determined using the univariate and multivariate analysis of the Cox model. The Kaplan-Meier survival analysis was performed, and pairs of survival curves based on the key factors were compared using the log-rank test.

Results: The ADC_{30} , ADC_{median} , ADC_{max} , $RADC_{30}$, $RADC_{median}$, and $RADC_{max}$ were significantly larger in the progressive group than in the stable group ($P < 0.05$). The median progression-free survival (PFS) was 22.9 months for all patients. The mean PFS for the stable and progressive groups were 47.7 ± 1.3 and 9.8 ± 1.3 months, respectively. Univariate analysis indicated that $RADC_{10}$, $RADC_{30}$, and $RADC_{median}$ were significantly correlated with the PFS [hazard ratio (HR)=31.02, 43.84, and 44.29, respectively, $P < 0.05$ for all]. Multivariate analysis showed that $RADC_{median}$ was the only independent predictor of tumor progression ($P = 0.04$). And the cutoff value of $RADC_{median}$ was 0.71.

Conclusions: Pre-RFA ADC histogram analysis might serve as a useful biomarker for predicting tumor progression and survival in patients with HCC treated with RFA.

Keywords: Diffusion-weighted imaging; apparent diffusion coefficient; histogram analysis; hepatocellular carcinoma; radiofrequency ablation; survival time

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world (1), and the second leading cause of cancer-related deaths in China (2). Currently, hepatic resection (HR) and radiofrequency ablation (RFA) are the accepted first-line treatment options for patients with early HCC according to the guidelines from European Association for the Study of the Liver and American Association for the Study of Liver Diseases (3). However, a majority of HCC patients are not candidates for surgery because of poor liver function or the presence of advanced disease. Recently, RFA has evolved as one of the most important therapeutic options for HCC (3,4). It is a minimally invasive, safe and effective technique and relatively easy to perform. However, a major shortcoming of RFA is the higher rate of local tumor recurrence compared to HR (5,6). Many previous studies have focused on the post-treatment responses of RFA in HCC (6,7). Development of an image-marker to noninvasively predict post-treatment response would significantly impact treatment decisions, and support personalized treatment approaches. Therefore, predicting the efficacy of RFA in HCC patients prior to the RFA treatment is important.

Diffusion weighted imaging (DWI) quantitatively evaluates the response to cancer therapy from changes in apparent diffusion coefficients (ADC). These changes occur early, and are apparent before any changes in tumor morphology (1,8). DWI was employed in Liver Reporting & Data System (LI-RADS™) to demonstrate HCC diagnosis, and T2 and triple phase enhanced images (9). Furthermore, ADC histogram analysis could quantify the distribution of signal intensity of voxels within a tumor by using routinely acquired clinical DWI data, which reflect the tumor heterogeneity (10-12). Many studies have reported that heterogeneity was highly correlated with treatment prediction, and in mathematical methods used in the heterogeneity evaluation, histogram analysis was widely used, and percentile values were useful (13,14).

Previous studies have demonstrated that ADC histogram analysis was effective for diagnosis, evaluation of biologic aggressiveness, and prediction of therapy response in glioblastoma, testicular germ cell tumors and colorectal hepatic metastases (10,11,14). However, little is known regarding its role in the prediction of therapeutic outcomes for RFA in HCC. The purpose of our study was to predict therapeutic effects of RFA treatment on HCC patients using ADC histogram parameters obtained before RFA

treatment, and determine key parameters that can best predict the efficacy of RFA treatment.

Materials and methods

Patients

The study group included HCC patients treated with RFA at National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences between January 2011 and October 2016. Inclusion criteria were as follows: 1) recent diagnosis of HCC with a single lesion on liver confirmed by biopsy; 2) treatment with RFA only; 3) magnetic resonance imaging (MRI) examination including DWI within 1 week prior to the treatment; 4) regular follow-up by MRI or CT; 5) Child-Pugh grade A or B; 6) no evidence of portal vein thrombus on MRI; and 7) no radiological evidence of lymph nodes or hematogenous metastasis. Exclusion criteria were lesions less than 1 cm, or degraded DWI images that prevent calculation of ADC (*Figure 1*). The study was approved by the Institutional Review Board of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences. The requirement for signed informed consent was waived for all patients as all data were collected for routine clinical management, and reviewed retrospectively.

Patients characteristics and clinical data

Clinical and pathological data including gender, age at the time of diagnosis, and tumor location (left, right, or caudate lobe) were collected for analysis. Venous blood samples were collected for plasma alpha-fetoprotein (AFP) and transferrin (TFN) measurement one week before the RFA treatment. Based on normal ranges and diagnostic values for HCC used at National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, two levels of AFP values were defined as negative ≤ 7 ng/mL and positive > 7 ng/mL. And the category of TFN was classified as positive > 190 ng/mL and negative ≤ 190 ng/mL.

Patient groups and follow-up

All patients were regularly followed-up using MRI or CT once in every 2–3 months until the progression of tumor or death or until the last follow-up time (October 15, 2016). The patients were grouped into a progressive group and a stable group according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1). The stable group included

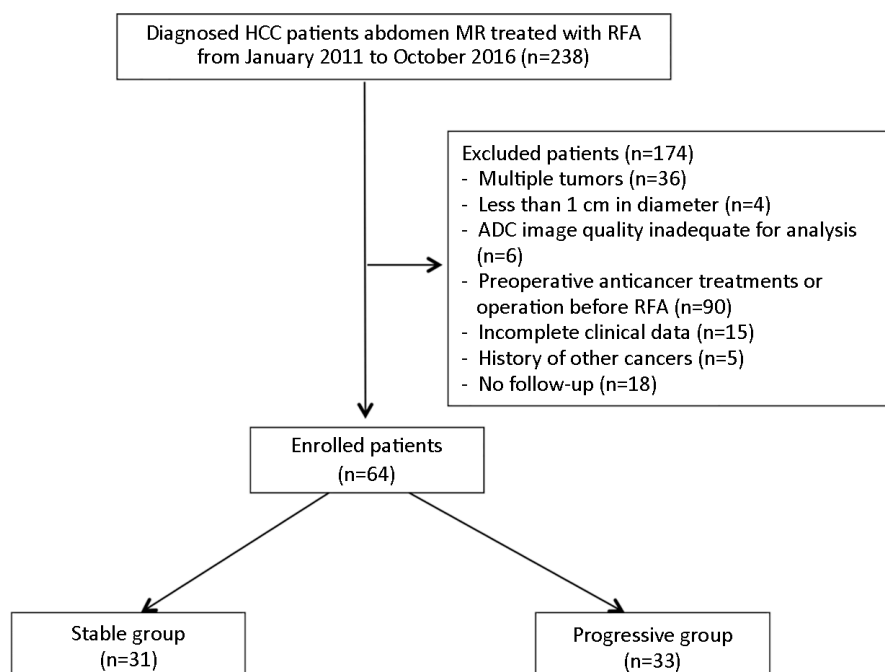


Figure 1 Flowchart of enrolled patients in our study. HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; ADC, apparent diffusion coefficient.

patients with complete response (CR), with disappearance of all target lesions and partial response (PR), with at least a 30% decrease in the sum of the longest diameter of the target lesions, with the baseline sum of the longest diameter as a reference. The progressive group included patients with stable disease (SD) with no sufficiently shrunken lesions to qualify for the PR or no sufficiently increased lesions to qualify for the progressive disease, and with progressive disease (PD), with at least a 20% increase in the sum of the longest diameter of the target lesions, taking the smallest sum of the baseline longest diameter as a reference.

MRI

MRI was performed using Signa Excite 3.0 T HDxt MR scanner (GE Healthcare, Milwaukee, USA) with an eight-element phased-array body coil. All patients entered the machine in the supine, feet first position. The MR sequences included: 1) breath-hold fat-saturated, fast recovery, fast spin-echo (FRFSE-FS) T1-weighted imaging in the axial plane [TR/TE: 250/2.9 ms, field of view (FOV): 34–38 cm, slice thickness/space: 5.0/0.5 mm, matrix size: 288×192, NEX: 1]; 2) FRFSE-FS T2-weighted imaging in the axial plane (TR/TE: 7,000/100 ms, FOV: 34–38 cm, slice thickness/space: 5.0/0.5 mm, matrix size: 288×224,

NEX: 2); and 3) breath-hold DWI with an axial single-shot spin echo, echo-planar imaging (EPI) sequence with DW gradients (b value 0 and 800 s/mm²) applied in three orthogonal directions (TR/TE: 2,500/65 ms, slice thickness/space: 6.0/2.0 mm, FOV: 34–38 cm, matrix size: 128×128, NEX: 2, and scan time 20–24 s). Positioning parameters were duplicated for T2-weighted image parameters to ensure image consistency.

RFA treatment

All patients were treated using local anesthesia in combination with intra-venous sedation. A B-type ultrasound-guided percutaneous RFA was performed using an ALOKA $\alpha 7$ B-type ultrasound system with a 9133 probe (2–6 MHz). We used the RITA Model 1500X radiofrequency (RF) generator (USA) in this study. All RFA procedures were performed by the same physician.

ADC histogram analysis

The DWI images were analyzed and processed by an experienced radiologist with more than 5 years of experience in abdominal MRI diagnosis. The T1WI/FS and T2WI/FS sequences were used to determine the lesion location, its maximum sectional area and maximal tumor

diameter (MTD). The regions of interest (ROI) were drawn by manually delineating the tumor slice by showing the maximum cross sectional image. A fixed-size ROI (250 mm²) was drawn on the non-lesion area in a relatively normal liver area at least 3 cm away from the lesion, avoiding the intrahepatic bile duct and blood vessels. The DWI images were transferred to an AW4.4 workstation (GE healthcare). ADC maps were created by fitting of a mono-exponential function in the “Functool” work package. Histograms of the ADC distribution maps were generated by the “X-section” function of commercial Volume View software. The ADC histogram was quantified by generating percentile values from the cumulative histogram for each patient, averaging from the lowest measured ADC value to the 10th, 30th, 50th, and 100th percentile for each patient separately (ADC₁₀, ADC₃₀, ADC_{median} and ADC_{max}) (Figure 2,3). The ratios of ADC₁₀, ADC₃₀, ADC_{median} and ADC_{max} to the mean ADC of the non-lesion area were calculated (RADC₁₀, RADC₃₀, RADC_{median} and RADC_{max} respectively).

Statistical analysis

The Kolmogorov-Smirnov test was used to evaluate whether the continuous variables were normally distributed. The student's *t*-test was used to compare continuous variables under the normal distribution between the stable and progressive groups, and Kruskal-Wallis test for data being not subject to normal distribution. Categorical variables were compared using the Fisher's exact test. For the calculation of PFS, disease

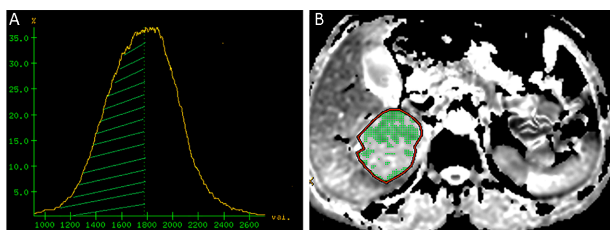


Figure 2 Representative image from a 62-year-old female in progressive group before radiofrequency ablation (RFA) treatment for hepatocellular carcinoma (HCC). (A) Apparent diffusion coefficient (ADC) histogram image. The area covered by green shadow is the ADC_{median} area; (B) ADC image shows the maximum section area. The whole lesion is the regions of interest (ROI), and the green shadow inside is the ADC_{median} area. The ROI area of the lesion at the posterior right lobe of liver is 2,211 mm², lesion ADC_{max}=1.77×10⁻³ mm²/s, ADC_{median}=1.56×10⁻³ mm²/s and RADC_{median}=0.74.

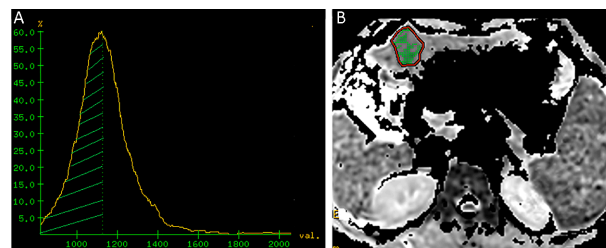


Figure 3 Representative image from a 49-year-old male in stable group before radiofrequency ablation (RFA) treatment for hepatocellular carcinoma (HCC). (A) Apparent diffusion coefficient (ADC) histogram image. The area covered by green shadow is the ADC_{median} area; (B) ADC image shows the maximum sectional area. The regions of interest (ROI) covers the whole lesion, and the green shadow inside is the ADC_{median} area. The ROI area of the lesion at the posterior right lobe of liver is 643 mm², lesion ADC_{max}=1.24×10⁻³ mm²/s, ADC_{median}=1.04×10⁻³ mm²/s, and RADC_{median}=0.68.

progression defined by RECIST 1.1 or death was used as an endpoint. The median PFS for all patients was calculated. The time interval of PFS was defined as the time between diagnosis of HCC and the date of imaging study just before identification of disease progression by imaging or death. The significant factors on disease progression were obtained by using the Cox model of univariate analysis. For factors with statistical significance, the Cox model of multivariate forward regression was used to identify key factors for predicting disease progression. Key factors were divided into two groups by using the median value, and the survival curves were plotted using the Kaplan-Meier method. The log-rank test was used to compare the pairs of survival curves based on key factors. Statistical significance was accepted at P<0.05 for all tests. All analyses were performed using SPSS software (Version 13.0; SPSS Inc., Chicago, IL, USA), except the multivariate model, which used the R software (Version 3.4.1; R Foundation for Statistical Computing, Vienna, Austria, <http://www.r-project.org/>) to evaluate its effectiveness.

Results

Patient characteristics

Sixty-four patients met the inclusion criteria and 174 patients were excluded from the analysis, which was shown in the flowchart in Figure 1. The stable group consisted 31 patients (25 males and 6 females, age range: 43–81 years, left lobe: 8 patients, and right lobe: 23 patients). The

disease progression group comprised 33 patients (23 males and 10 females, age range: 44–84 years, left lobe: 5 patients, and right lobe: 28 patients).

ADC parameters

The ADC₃₀, ADC_{median}, ADC_{max}, RADC₃₀, RADC_{median} and RADC_{max} were significantly larger in the progressive group than in the stable group ($P < 0.05$; Table 1). There were no significant differences in the age, MTD, ADC₁₀ and RADC₁₀ between the two groups ($P > 0.05$, Table 1). The categorical variables of AFP and TFN were not significantly different between the two groups ($P = 1.00$, $P = 0.62$) (Table 1). In the progressive group, the MTD range was 0.5–6.9 cm with the median MTD of 2.6 cm. In the stable group, the MTD range was 0.5–7.1 cm with the median MTD of 2.7 cm.

Correlation between significant ADC histogram parameters and PFS

The survival curve showed that RADC₁₀, RADC₃₀ and RADC_{median} were correlated with PFS (Figures 4–6). In the univariate analysis, RADC₁₀, RADC₃₀ and RADC_{median} had a significant impact on PFS ($P = 0.04$), and the hazard ratio

(HR) values were 31.02, 43.84 and 44.29, respectively. Other factors including age, gender, MTD, AFP, ADC₁₀, ADC₃₀, ADC_{median}, ADC_{max} and RADC_{max} had no significant impact on PFS ($P > 0.05$, Table 2). In addition, the median PFS from all patients was 22.9 months (95% CI, 16.7–29.2). The mean PFS for the stable and progressive group were 47.7 ± 1.3 and 9.8 ± 1.3 months, respectively.

Key factor for PFS of RFA in HCC

The multivariate forward analysis of RADC₁₀, RADC₃₀ and RADC_{median} showed that RADC_{median} had an independent significant impact on PFS ($\chi^2 = 4.12$, $P = 0.04$). The mean of C-index of the multivariate model was 0.617 [standard error (SE) = 0.056]. The RADC₁₀, RADC₃₀ and RADC_{median} value could be divided into two groups by using the median value of 0.60, 0.67 and 0.71, respectively ($\chi^2 = 1.17$, 2.68 and 5.12; $P = 0.28$, 0.10 and 0.02). The average PFS was 20.71 ± 3.41 months in the RADC_{median} group with a value ≥ 0.71 (95% CI, 23.39–35.91), and 26.65 ± 3.19 months in the RADC_{median} group with a value < 0.71 (95% CI, 14.02–27.41) (Figures 4–6).

Table 1 Comparison between stable and progressive groups before RFA treatment for HCC

Variables	Stable group (n=31) ($\bar{x} \pm s$)	Progressive group (n=33) ($\bar{x} \pm s$)	P	t/z
Age (year)	61.50±9.80	59.20±9.90	0.35	0.94
MTD (cm)	2.7±1.4	2.6±1.3	0.79	0.27
AFP [n (%)]			1.00#	
Negative	27 (42.19)	28 (43.75)		
Positive	4 (6.25)	5 (7.81)		
TFN [n (%)]			0.62#	
Negative	11 (17.19)	14 (21.87)		
Positive	20 (31.25)	19 (29.69)		
ADC ₁₀	0.79±0.16	0.88±0.21	0.06	-1.92
ADC ₃₀	0.89±0.17	0.99±0.19	0.03*	-2.19
ADC _{median}	0.95±0.18	1.06±0.20	0.03*	-2.28
ADC _{max}	1.12±0.21	1.22±0.22	0.04*	-1.95
RADC ₁₀	0.57±0.09	0.62±0.11	0.08	-1.77
RADC ₃₀	0.64±0.09	0.69±0.09	0.03*	-2.26
RADC _{median}	0.68±0.10	0.74±0.08	0.02*	-2.50
RADC _{max}	0.80±0.10	0.86±0.09	0.02*	-2.33

RFA, radiofrequency ablation; HCC, hepatocellular carcinoma; MTD, maximal tumor diameter; AFP, alpha-fetoprotein; TFN, transferrin; ADC, apparent diffusion coefficient; RADC, non-lesion area ADC; #, categorical variables were compared using the Fisher's exact test; *, ADC values are in units of $10^{-3} \text{ mm}^2/\text{s}$.

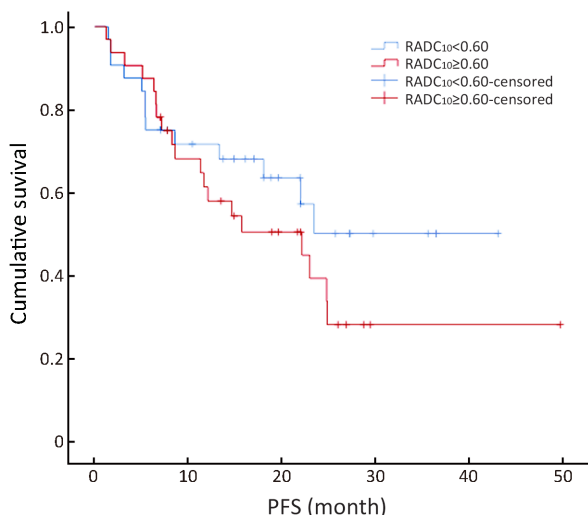


Figure 4 Ratio of apparent diffusion coefficient (ADC)₁₀ to the mean ADC of the non-lesion area (RADC₁₀) value could be divided into two groups using the median value (0.60) as the boundary value ($\chi^2=1.17$, $P=0.28$).

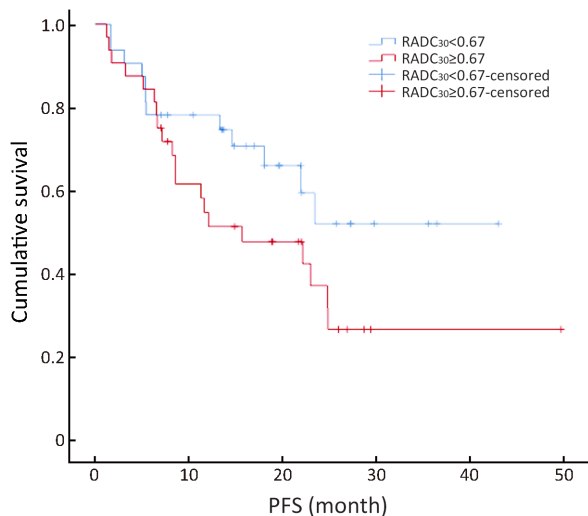


Figure 5 Ratio of apparent diffusion coefficient (ADC)₃₀ to the mean ADC of the non-lesion area (RADC₃₀) value could be divided into two groups using the median value (0.67) as the boundary value ($\chi^2=2.68$, $P=0.10$).

Discussion

Our study showed that baseline ADC and RADC values were significantly different between the progressive and stable groups suggesting that ADC and RADC values might be useful predictive biomarkers prior to RFA in HCC patients. Previous studies focused on the evaluation

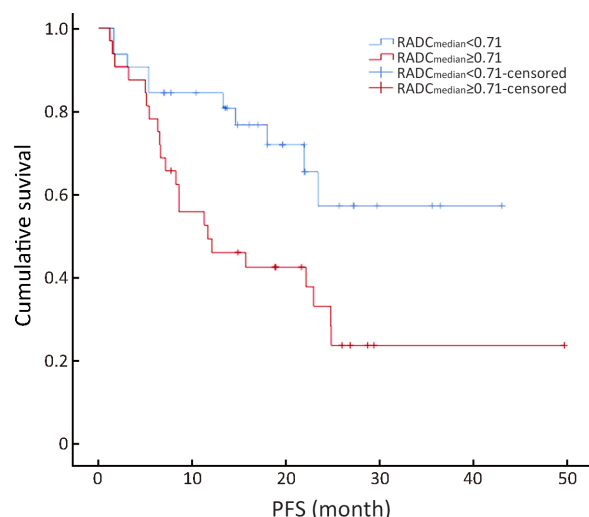


Figure 6 Ratio of apparent diffusion coefficient (ADC)_{median} to the mean ADC of the non-lesion area (RADC_{median}) value could be divided into two groups using the median value (0.71) as the boundary value ($\chi^2=5.12$, $P=0.02$). The average disease progressive-free survival (PFS) was 20.71 ± 3.41 months in the RADC_{median} group with a value ≥ 0.71 [95% confidence interval (95% CI), 23.39–35.91], and 26.65 ± 3.19 months in the RADC_{median} group with a value < 0.71 (95% CI, 14.02–27.41).

of RFA efficacy and monitoring recurrence after the RFA treatment (6,7). However, a proper evaluation method for predicting the therapeutic efficacy before RFA is urgently needed. This is important to provide indications for clinical project selection and prognostic prediction. Therefore, our findings might offer insights into evaluation of RFA treatment in HCC.

We also demonstrated that the ADC and RADC values before the RFA were larger in the progressive group than in the stable group, and the higher pre-treatment ADC and RADC values were associated with the shorter PFS. Previous studies (15-17) have found that in HCC patients, high ADC values prior to transcatheter arterial chemoembolization (TACE) or chemotherapy were related to poor prognosis. Furthermore, Dong *et al.* (17) showed that ADC values before TACE were negatively correlated with survival. Our findings were in agreement with these reports (15-17). The reason for high ADC values observed in our study may be as follows. There is a negative correlation between a tumor ADC value and cell density (18). When the cell density increases, the extracellular space decreases, limiting the diffusion of water molecules, and thus the ADC values decrease accordingly. Cell density

Table 2 Impact of different factors on PFS before RFA treatment for HCC

Variables	β	SE	Wald value	HR	95% CI	P
Gender	-0.53	0.43	1.54	0.59	0.25–1.36	0.22
Age (year)	-0.04	0.02	2.90	0.97	0.93–1.01	0.09
MTD (cm)	-0.07	0.14	0.23	0.94	0.72–1.23	0.64
AFP (ng/mL)	0	0	0.92	1.00	1.00–1.01	0.34
TFN (ng/mL)	0	0	0.32	1.00	0.99–1.03	0.57
ADC ₁₀	0	0	2.79	1.00	1.00–1.01	0.09
ADC ₃₀	0	0	2.29	1.00	0.97–1.02	0.13
ADC _{median}	0	0	1.92	1.00	0.98–1.01	0.17
ADC _{max}	0	0	0.77	1.00	0.99–1.02	0.38
RADC ₁₀	3.44	1.78	3.73	31.02	1.01–101.32	0.04*
RADC ₃₀	3.78	1.91	3.91	43.84	1.03–185.90	0.04*
RADC _{median}	3.79	1.91	3.92	44.29	1.04–198.74	0.04*
RADC _{max}	2.93	1.92	2.34	18.72	0.44–80.11	0.13

The Cox model of univariate analysis, $n=64$, $\alpha=0.05$. PFS, progression-free survival; RFA, radiofrequency ablation; HCC, hepatocellular carcinoma; MTD, maximal tumor diameter; AFP, alpha-fetoprotein; TFN, transferrin; ADC, apparent diffusion coefficient; RADC, non-lesion area ADC; β , regression coefficient; SE, standard error; HR, hazard ratio; 95% CI, 95% confidence interval. *, ADC values are in units of $10^{-3} \text{ mm}^2/\text{s}$.

is a significant indicator of cellular differentiation and malignancy of the tumor (18). Hence, the ADC value might reflect the degree of malignancy to some extent. However, there were discrepancies in association between ADC values and response to therapy in these studies because of marked differences in tumor types, treatment modalities, chemotherapeutic agents, and methods to analyze the data. Further studies with large-scale and long-term follow-up will be needed to explain high ADC values observed in HCC patients.

The RADC₁₀, RADC₃₀ and RADC_{median} but not ADC had a significant impact on PFS. Many factors influence ADC value, especially in the liver including blood supply, tumor localization and cirrhosis. The liver has a dual blood supply; it receives blood from both the hepatic artery and portal vein. In this study, most patients had mild to moderate cirrhosis. These factors affect background ADC values in the liver. To compensate for these effects, ADC values measured in the lesion were compared with the ADC values in non-lesion areas calculating RADC values. The RADC value was a reference index that could more objectively reflect the real status of the lesions. Our results supported that the RADC values of HCC lesions could predict patients' response to RFA.

We found that not only RADC had the predictive power, but also RADC_{median} was the only independent predictor of our outcome. Using 0.71 as the cutoff value of RADC_{median}

to segment our subjects into two groups, we found that PFS was reduced in the group with high RADC_{median} values. Furthermore, consistent with previous studies, RADC_{median} was negatively correlated with PFS (16,19).

Previously, Moffat *et al.* (19) reported that it was not possible to reflect tumor heterogeneity using changes in average ADC value to evaluate the efficacy of HCC intervention. Future studies should use RADC_{median} value in patients receiving treatments other than RFA like TACE. Furthermore, RADC_{median} value could be used to evaluate treatment efficacy in other tumors.

Interestingly, our results demonstrated that gender, age and tumor MTD had no significant effect on the PFS. Previous studies by Heo *et al.* (20) on the predictive value of ADC for cervical cancer showed that a variety of clinical factors (including age, MTD, tumor stage and pelvic lymph node metastasis) had a limited predictive value on the efficacy of cervical cancer treatment. The authors (20) suggested that the pattern of disease progression generally rely on the biologic heterogeneity of the tumor itself. Therefore, functional MRI techniques that reflect internal characteristics of the tumor were valuable.

In previous studies, Kao *et al.* (21) showed that patients with higher preoperative AFP levels had poorer prognosis after microwave ablation treatment. Furthermore, Zaitso *et al.* (22) reported that the survival rates of patients who had serum TFN levels of 190 mg/dL or more were

significantly higher than those of patients with lower TFN levels. However, we found that pre-treatment plasma AFP and TFN had no significant impact on PFS. This was supported by a previous study (23), which showed that decreased AFP level was significantly correlated with tumor regression in less than 1/3 of HCC patients.

This study had some limitations. First, we had a relatively small sample size. Second, there were artifacts in the DWI because currently DWI spatial resolution was relatively poor (8). Third, in 4 patients, the ADC histograms were not sharp to measure lesions smaller than 1 cm in diameter, and DWI artifacts affected the observation and measurement of lesions in 6 patients. Lastly, the boundary $RADC_{median}$ value was identified by the median value. An improved analysis with a larger cohort might identify another metric using the receiver operating characteristic (ROC) curve.

Conclusions

We showed that use of histogram analysis to extract ADC features associated with heterogeneous ADC distributions improve the predictive power of DWI in HCC patients treated with RFA. The $RADC_{median}$ value might be a potential biomarker for predicting treatment efficacy of RFA in HCC patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Yuan Z, Li WT, Ye XD, et al. Novel functional magnetic resonance imaging biomarkers for assessing response to therapy in hepatocellular carcinoma. *Clin Transl Oncol* 2014;16:599-605.
2. Chen W, Sun K, Zheng R, et al. Cancer incidence and mortality in China, 2014. *Chin J Cancer Res* 2018;30:1-12.
3. Xu XL, Liu XD, Liang M, et al. Radiofrequency ablation versus hepatic resection for small hepatocellular carcinoma: systematic review of randomized controlled trials with meta-analysis and trial sequential analysis. *Radiology* 2018;287:461-72.
4. Lee YH, Hsu CY, Chu CW, et al. Radiofrequency ablation is better than surgical resection in patients with hepatocellular carcinoma within the Milan criteria and preserved liver function: a retrospective study using propensity score analyses. *J Clin Gastroenterol* 2015;49:242-9.
5. Pompili M, Saviano A, de Matthaeis N, et al. Long-term effectiveness of resection and radiofrequency ablation for single hepatocellular carcinoma ≤ 3 cm. Results of a multicenter Italian survey. *J Hepatol* 2013;59:89-97.
6. Gory I, Fink M, Bell S, et al. Radiofrequency ablation versus resection for the treatment of early stage hepatocellular carcinoma: a multicenter Australian study. *Scand J Gastroenterol* 2015;50:567-76.
7. Gordic S, Corcuera-Solano I, Stueck A, et al. Evaluation of HCC response to locoregional therapy: Validation of MRI-based response criteria versus explant pathology. *J Hepatol* 2017;67:1213-21.
8. Taouli B, Koh DM. Diffusion-weighted MR imaging of the liver. *Radiology* 2010;254:47-66.
9. Elsayes KM, Hooker JC, Agrons MM, et al. 2017 Version of LI-RADS for CT and MR Imaging: An Update. *Radiographics* 2017;37:1994-2017.
10. Kondo M, Uchiyama Y. Apparent diffusion coefficient histogram analysis for prediction of prognosis in glioblastoma. *J Neuroradiol* 2018;45:236-41.
11. Min X, Feng Z, Wang L, et al. Characterization of testicular germ cell tumors: Whole-lesion histogram analysis of the apparent diffusion coefficient at 3T. *Eur J Radiol* 2018;98:25-31.
12. Xu XQ, Li Y, Hong XN, et al. Radiological indeterminate vestibular schwannoma and meningioma in cerebellopontine angle area: differentiating using whole-tumor histogram analysis of apparent diffusion coefficient. *Int J Neurosci* 2017;127:183-90.
13. Hempel JM, Schittenhelm J, Bisdas S, et al. *In vivo* assessment of tumor heterogeneity in WHO 2016 glioma grades using diffusion kurtosis imaging:

- Diagnostic performance and improvement of feasibility in routine clinical practice. *J Neuroradiol* 2018;45:32-40.
14. Liang HY, Huang YQ, Yang ZX, et al. Potential of MR histogram analyses for prediction of response to chemotherapy in patients with colorectal hepatic metastases. *Eur Radiol* 2016;26:2009-18.
 15. Wu XM, Wang JF, Ji JS, et al. Evaluation of efficacy of transcatheter arterial chemoembolization for hepatocellular carcinoma using magnetic resonance diffusion-weighted imaging. *Onco Targets Ther* 2017;10:1637-43.
 16. Yuan Z, Li WT, Peng WJ. Pre-treatment apparent diffusion coefficient is imaging biomarker for prediction of response to chemoembolization in hepatocellular carcinoma. *Eur J Radiol* 2013;82:e901-2.
 17. Dong S, Ye XD, Yuan Z, et al. Relationship of apparent diffusion coefficient to survival for patients with unresectable primary hepatocellular carcinoma after chemoembolization. *Eur J Radiol* 2012;81:472-7.
 18. Gibbs P, Liney GP, Pickles MD, et al. Correlation of ADC and T2 measurements with cell density in prostate cancer at 3.0 Tesla. *Invest Radiol* 2009;44:572-6.
 19. Moffat BA, Chenevert TL, Lawrence TS, et al. Functional diffusion map: a noninvasive MRI biomarker for early stratification of clinical brain tumor response. *Proc Natl Acad Sci USA* 2005;102:5524-9.
 20. Heo SH, Shin SS, Kim JW, et al. Pre-treatment diffusion-weighted MR imaging for predicting tumor recurrence in uterine cervical cancer treated with concurrent chemoradiation: value of histogram analysis of apparent diffusion coefficients. *Korean J Radiol* 2013;14:616-25.
 21. Kao WY, Chiou YY, Hung HH, et al. Serum alpha-fetoprotein response can predict prognosis in hepatocellular carcinoma patients undergoing radiofrequency ablation therapy. *Clin Radiol* 2012;67:429-36.
 22. Zaitzu J, Yamasaki T, Saeki I, et al. Serum transferrin as a predictor of prognosis for hepatic arterial infusion chemotherapy in advanced hepatocellular carcinoma. *Hepatol Res* 2014;44:481-90.
 23. Colli A, Fraquelli M, Casazza G, et al. Accuracy of ultrasonography, spiral CT, magnetic resonance, and alpha-fetoprotein in diagnosing hepatocellular carcinoma: a systematic review. *Am J Gastroenterol* 2006;101:513-23.

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