ORIGINAL ARTICLE

Added value of diffusion weighted MRI in evaluation of treatment response: post radiofrequency ablation for hepatocellular carcinoma

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KEYWORDS
Diffusion-weighted MRI; Apparent diffusion coefficient; Radiofrequency ablation; Hepatocellular carcinoma; Local tumor progression

Abstract  Objective: To evaluate the feasibility of DWI and the corresponding ADC values to detect local tumor progression (LTP) after radiofrequency ablation for hepatocellular carcinoma. Materials and methods: 139 MR examinations were done for 51 HCC patients post-RFA. Pre and postgadolinium enhanced images as well as DW sequences were performed. ADC values of ablation zones and liver parenchyma were assessed. ADC values of ablation zones and adjacent signal alterations identified in DWI were analyzed. Results: LTP was detected in 12 patients (23.5%) and 16 lesions (21.9%). The mean ADC value of ablated zones differed significantly from that of normal liver parenchyma. No obvious changes were detected in the ADC values of the ablated zones over time. ROIs covering the whole ablation zone showed no significant ADC value difference regarding the presence or absence of LTP. DWI showed 53 hyperintense areas in the periphery of the ablated zones, and the corresponding ADC values were significantly lower in patients with LTP than in patients without LTP. Conclusion: DWI is a feasible follow-up tool for postablation liver contributing in detection of LTP. ADC based evaluation of signal alterations in the periphery of the ablation zone may be helpful in differentiation between LTP and post treatment tissue changes.

1. Introduction

Hepatocellular carcinoma (HCC) is a major global health problem with an estimated incidence ranging between 500,000 and 1,000,000 new cases annually (1).

During the past two decades, liver transplantation and partial hepatectomy have been considered the main curative...
Radiofrequency ablation (RFA) has become a widely used treatment for HCC with some studies reporting significant long-term survival results (4).

For several years magnetic resonance imaging (MRI) has been used for the evaluation of treatment response in malignant liver lesions (5). However, the assessment of tumor response remains difficult. Residual contrast enhancement may also be difficult to appreciate (6). Furthermore, focal liver lesions treated by RF ablation often contain a hypersignal on T1-weighted MR sequences, corresponding to coagulation necrosis, which makes any residual tumoral contrast enhancement difficult to be differentiated (7).

Diffusion-weighted MRI (DW-MRI), primarily performed in neuroradiology for acute stroke, has then been introduced into abdominal imaging representing a supplementary tool for detecting and characterizing hepatic lesions (8).

Based on the calculation of apparent diffusion coefficients (ADC), DWI allows for characterization of biological tissue on the basis of its water diffusion properties that are determined by the microstructure organization, cell density, and viability of the tissue (9).

Studies investigating time-related image characteristics and histopathological findings after hepatic RF ablation identified typical changes in the microstructure of the coagulation zone (10).

It is a challenge to improve follow-up imaging identifying any residual tumor or tumor regrowth, called local tumor progression (LTP) as early as possible.

The aim of the current study was to evaluate time-related diffusion alterations after hepatic RF ablation giving an added value in diagnosis of viable HCC tumor for early detection of LTP.

2. Materials and method

This prospective study was conducted during the period between February 2012 and November 2014 at the Radiodiagnosis Department, Ain Shams University on 51 patients (34 males and 17 females, mean age 54), suffering from HCC, who are candidates for radiofrequency ablation and already underwent the procedure. Written and verbal consents were obtained from all patients as well as an agreement of the local ethics committee.

Exclusion criteria:

Patients with MRI incompatible devices such as cardiac pacemaker, metallic valves, hearing aids or aneurismal clips.

2.1. RF ablation system

Radiofrequency ablations were performed under ultrasound (US) guidance. Patients were treated under general sedation. A Covidien/Valley Lab RF ablation system (RF Ablation System, E series, Covidien/Valley Lab, Boulder, CO, USA) was used to deliver RF ablation energy to the targeted lesions.

Single, clustered, or multiple cooled electrodes (Cool-Tip Ablation electrodes) were used according to the size and shape of the tumor to be treated. Radiofrequency energy was applied from 12 to 15 min, according to the manufacturer’s recommendations, with automated control of the impedance.

Radiofrequency ablations were considered successful when the temperature in the lesion was 70°C or higher. Patients were discharged the day following the procedure.

2.2. MR study

Follow-up MR is systematically scheduled one month after the RF intervention then every 3 months for 1 year, and from thereon every 6 months. Additional follow-up examinations are performed depending on the individual course of the disease.

2.2.1. Patients preparation

No preparation was done. The patients were sent for follow-up at the MRI unit, Radiodiagnosis Department in Ain Shams University Hospital.

2.2.2. MR protocol

Magnetic resonance imaging examinations were performed on a Philips Intera Achieva 1.5 T super conducting MR unit (Philips Medical Systems, the Netherlands), with a 16-channel body coil.

Breath-hold T1-weighted image and single shot fast spin echo (SSFSE) T2 weighted images were obtained. Diffusion weighted images were obtained before contrast administration with b values of 0, 500, and 1000 s/mm². Breath-hold, dynamic 3D T1 weighted sequence was performed after DWIs (bolus injection of 0.1 mmol/kg gadopentetate dimeglumine 2 ml/s) followed by flush saline. All DWIs were obtained in transverse plane using single-shot echo-planar spin echo sequences. Imaging parameters for DWIs were: TR: 1200 ms; TE: 90 ms; FOV: 38 cm × 38 cm (change according to body size); number of excitation: 1; matrix size: 192 × 192; section thickness: 4 mm; intersection gap: none. DW sequences required a total of 2 min to scan on MR.

2.3. MR analysis

2.3.1. Image analysis and ADC measurements

All MR images were reviewed on a commercial workstation (HPZR 24 W Easy Vision; Philips Medical Systems workstation). The reviewers were blinded to the course of ablation, MR reports, clinical history and follow-up results.

DW images of each patient were reviewed before the standard MR examination including T1-, T2-weighted, and the dynamic series of gadolinium-enhanced images. Ablation size was assessed in T1, DWI (b = 0) and contrast-enhanced T1 by the measurement of the largest long and short axes of the coagulated area.

ADC of each ablation zone was measured by drawing a free hand region of interest (ROI) around the outlines of each ablation zone on the DWI (b = 0 s/mm²) images. ROIs were then automatically transferred to the ADC map and the corresponding ADC value of the ablation zone was registered.
For the evaluation of normal surrounding liver, circular ROIs (at least 10 mm in diameter) were drawn within normal liver parenchyma (subsegment 6 if possible) by carefully avoiding large vascular and biliary structures larger than 3 mm. The examinations were grouped in control intervals (according to the interval between RF procedure and follow-up MR examination) in order to identify changes of the ablation’s ADC values over time. ADC values of the ablation zones were analyzed statistically regarding presence of LTP.

2.3.2. Signal alteration in the periphery of the ablation zone

The periphery of the ablation zone was analyzed in the DW images with regard to signal abnormalities. If a focal area of hyperintensity was detected adjacent to the ablation zone in the b = 0 image, which did not decrease in images with higher b-value, it was considered suspicious for LTP and the corresponding ADC value of the area was recorded by drawing a ROI that completely covered the hyperintense area which was copied and pasted from the DW image to the ADC map.

The ADC ratio (ADC hyperintense area/ADC liver) was calculated in order to minimize effects related to individually modified diffusion properties caused by underlying hepatic tissue changes, such as steatosis or fibrosis. The calculated ADC ratios were analyzed regarding presence of LTP.

2.3.3. Standard of reference

According to the current practice reported in the literature, the standard of reference for successful therapy was represented by all available follow-up imaging results, clinical history, and pathologic findings. Treatment result was grouped in “complete ablation” showing regular, nonenhancing rim of the ablation zone that is stationary or decreasing in size in the long-term follow-up (at least 12 months) and “LTP presenting new enhancement areas, increase in size and development of T1-weighted hypointense and T2-weighted hyperintense areas. The general observation period including imaging as well as clinical follow-up of the patients ranged between 13 and 25 months.

2.3.4. Statistical analysis

The analysis was done using the JMP software version 8.0. The Wilcoxon test was used to compare the ADC ratios. Significance level was set to 0.05.

3. Results

One hundred and thirty-nine consecutive follow-up MR examinations of 73 ablation zones in 51 patients were investigated. Table 1 shows a list of patients, ablated zones and their follow-up results.

### Table 1: List of patients, ablated zones and their follow-up results.

<table>
<thead>
<tr>
<th>Examinations</th>
<th>Ablated zones</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>139</td>
<td>73</td>
<td>51</td>
</tr>
<tr>
<td>No LTP</td>
<td>57</td>
<td>39</td>
</tr>
<tr>
<td>LTP</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>(78.1%)</td>
<td>(21.9%)</td>
</tr>
<tr>
<td></td>
<td>(76.5%)</td>
<td>(23.5%)</td>
</tr>
</tbody>
</table>

Absence of LTP at MR follow-up imaging (Fig. 1) was achieved in 39 of all 51 patients (76.5%). As regards the number of treated lesions per patient, the LTP occurred in 16 lesions (21.9%). Mean size of all ablations assessed by measurement of the largest long and short axis in the different sequences was: 3.8 cm × 2.5 cm in T1, 3.6 cm × 2.5 cm in postcontrast T1, and 3.3 cm × 2.3 cm in the b = 0 s/mm² images.

3.1. ADC values

The mean ADC value of normal liver parenchyma was 1.11 ± 0.26 × 10⁻³ mm²/s while that for the ablation zones was 1.26 ± 0.33 × 10⁻³ mm²/s. Significant difference in ADC between liver and ablation zones (P = 0.0004) was found after analyzing all the ADC values obtained during the whole study.

In the 139 examinations, 53 focal hyperintense areas at the periphery of the ablation zone were detected in the DW images. Most of the foci were detected within the first control examinations (<180 days after RF procedure). Fig. 3 shows interval detection of hyperintensities at the periphery of the ablated zones.

In 16 of the newly detected hyperintensities, LTP was confirmed at follow-up (Fig. 4).

In the other 37 lesions with hyperintensities, the majority of the foci disappeared over time: 26 of 37 (70.3%) were no longer detectable in the subsequent follow-up MR examination, whereas 11 of 37 (29.7%) persisted in subsequent MR examinations (mean time of persistence: 115 days ± 46 days) (Figs. 5 and 6).

The corresponding ADC values of the hyperintense areas were significantly lower in cases with LTP confirmed at follow-up than in cases without LTP (1.25 ± 0.31 × 10⁻³ mm²/s in cases with LTP versus 1.29 ± 0.35 × 10⁻³ mm²/s in cases without LTP).

The difference in ADC ratios of both groups confirmed statistical significance (P = 0.003).

4. Discussion

Treatment efficacy and ablative margin after RFA are conventionally evaluated by enhanced CT or MRI with dynamic study. Enhanced CT and MRI performed after RFA have some limitations. Benign periablational enhancement, which can be seen immediately and can last for up to 6 months after ablation, is difficult to differentiate from residual unablated tumor. Next, enhanced CT or MRI is not able to evaluate both the ablative margin and index tumors on identical images (11–13).
Fig. 1  Well ablated right hepatic lobe HCC. Images taken one month after RFA show right hepatic lobe segment VIII large well defined wedge shaped area eliciting high T1 (A) and low T2 (B) signal with no evidence of pathological enhancement through the dynamic arterial (C), porto-venous (D), delayed (E) images, no restriction in the DWI (F) with the ADC (G) maps showing high value ($1.28 \times 10^{-3}$ mm$^2$/s). No LTP was detected in the follow-up studies.
The diagnostic management of the post-RF ablation liver remains a challenging issue that is related to difficulties in accurately differentiating residual or recurrent vital tumor from nontumoral tissue changes following thermal therapy. DWI is increasingly applied in the evaluation of treatment effectiveness in the oncologic patient (14). DWI technique can provide qualitative and quantitative information about molecular tissue characteristics and may offer additional diagnostic information in the follow-up MR imaging after hepatic RF ablation (15).

In the present study the overall LTP rate of 21.9% (Table 1) is in accordance with values published in the literature (16). Several studies have been performed focusing on time-related histopathological changes after RF ablation, especially with regard to the differentiation between post-treatment tissue and residual or recurrent tumor tissue (17).

It could be shown in the present study, that the ablation zones can be differentiated from surrounding liver parenchyma visually in the DW images and by means of ADC maps in all patients. However analysis of ablation zones examined at different time points after the RF procedure revealed no significant changes in ADC values over time which agrees with Lu et al. (18) who in their study assessed the liver tumor response in the ablation zone after RF ablation found that the ADC value does not show significant changes over time.

The heterogeneous appearance of the ablation zone reflecting the different posttreatment tissue changes that can be found after RF ablation is mainly due to coagulative necrosis, hemorrhagic products, and dehydration (19).

The abovementioned changes are present at varying degree depending on the individual conditions in each patient. This may explain the finding that ADC values obtained from ROIs covering the whole ablation zone did not differ significantly regarding occurrence of LTP at follow-up; thus, it is not suitable to use the “ADC value of the entire ablation zone” as an indicator for LTP. If there are any measurable differences in the ADC values regarding LTP, those differences are masked by the heterogeneous appearance of the entire ablation zone produced by the varying posttreatment tissue changes.

Several studies (20,21) found that the LTP rate tends to be lower in HCC patients with an adequate ablation margin, it has to be considered that LTP mainly occurs in the periphery of the ablation zone which is often not completely included in the ROI, being drawn along the macroscopically visible contours of the ablation zone, thus it is very important to analyze the periphery of the ablation zone separately.

Abdominal DW images are less common than standard T1- and T2-weighted imaging and therefore may be difficult to interpret. Viable tumor regions appear hyperintense (bright) on DW images, whereas necrotic regions appear hypointense (dark) (9).

The present study indicates, that DWI may offer additional diagnostic possibilities in the follow-up after RF ablation. First, DW images could be used as a “screening sequence” because viable tumor regions and suspected areas in the periphery of the ablation zone could be identified more easily, and analyzed precisely in conjunction with the conventional T1, T2, and dynamic contrast-enhanced images.

Benign periablational enhancement surrounding the ablation zone is frequently found to show moderate to intense peripheral rim-like enhancement on the arterial phase of contrast-enhanced MRI which may persist on the delayed phase. This rim has low-signal intensity on T1-, and high-signal intensity on T2-weighted images. Histologic analysis of the perilesional rim has revealed that it is initially reactive hyperemia and subsequently fibrosis and a giant cell reaction (22).

The present study indicates that ADC maps could be helpful in the analysis of unclear hyperintense areas adjacent to the ablation zone differentiating between tumoral tissue and posttreatment changes. It could be demonstrated in this study, that unclear signal alterations in the periphery of the ablation zone exhibited markedly lower ADC values in patients with confirmation of LTP at follow-up. This is due to the fact that therapeutically induced nontumoral tissue changes (e.g., edema, inflammation, fibrosis, and necrosis) usually show low cellularity and therefore present with less signal in DWI (and high ADC, respectively), and can thereby be distinguished from tumoral tissue that presents with high signal in DWI (and low ADC value, respectively) (15). This is in accordance with Schraml et al. (23) and Kim et al. (24) who in their studies regarding the DW-MRI and ADC values for follow-up after RF ablation, found that ADC maps could be helpful for analyzing unclear hyperintense areas adjacent to the ablation zone.

Fig. 2 Mean ADC values of the ablation zones and liver at different time intervals after RF procedure.

Fig. 3 Interval detection of hyperintensities at the periphery of the ablated zones.
where differentiation between tumor tissue and post-treatment changes is unambiguous. It has been demonstrated that unclear signal alterations in the periphery of the ablation zone exhibited markedly lower ADC values in patients with local tumor progression on follow-up DW-MRI and in the ADC map.

**Fig. 4** Images obtained one month after RF ablation for HCC at subsegment 7, and the lesion appears hyperintense on T1 (A), hypointense on T2 (B), showing marginal enhancement persisting in the porto-venous phase (C). Its margin presents bright signal on DWI (D) and dark in the corresponding ADC (E) images, and the ADC value of the entire area revealed a relatively high value ($1.25 \times 10^{-3} \text{ mm}^2/\text{s}$); however studying the peripheral margin alone revealed significant low ADC values ($1.07 \times 10^{-3} \text{ mm}^2/\text{s}$). In long term follow-up it showed evidence of LTP. Ill defined marginal enhancement was noted at the anterior aspect of subsegment 8 appearing relatively bright on DWI, however not appreciated in the corresponding ADC, disappearing in long term follow-up which could represent transient hepatic intensity differences.
In the present study, a relatively high number of “false positive cases” were observed, with hyperintense areas being detected in the high $b$-value DW images, which did not correspond to LTP. This was also detected by Park et al. (25) who found that tumor necrosis intermingled with fibrotic component and inflammatory granulation tissues may show diffusion restriction, and can sometimes mimic viable tumor.

These encountered DW signal alterations could be ascribed to transient postinterventional perfusion inhomogeneities in the surrounding of the ablation zone and to postinterventional changes.

**Fig. 5** Images obtained one month after RF ablation for HCC at subsegment 5, the lesion appears hypointense on T1 (A) and T2 (B), and the margin appears hyperintense on T1. After gadolinium administration persistent marginal enhancement is noted in arterial phase (C) slightly decreasing in the porto-venous phase (D). DWI (E) presents marginal bright signal, however being not dark in the corresponding ADC (F) with high value ($1.27 \times 10^{-3} \text{ mm}^2/\text{s}$) denoting post therapy changes. In long term follow-up the marginal DWI bright signal disappeared showing no evidence of LTP.
bile duct irregularities with subsequent focal cholestasis. However, such processes are expected to be associated with high ADC values, so that the corresponding ADC maps should facilitate the differentiation from LTP.

This prospective study had two limitations. The limited spatial resolution of DWI, and the decreased significance of a ROI analysis. Thus, the use of ADC values derived from ROIs that include the entire ablation area may not adequately

**Fig. 6** Images obtained four months after RF ablation for HCC at subsegment 7, the lesion appears hyperintense on T1 (A) and isointense on T2 (B), and the margin appears hyperintense on T1. After gadolinium administration no appreciable enhancement seen in the arterial (C) nor porto-venous (D). DWI (D) presents marginal bright signal, however being also bright in the corresponding ADC (E) showing high value \((1.25 \times 10^{-3} \text{ mm}^2/\text{s})\). In long term follow-up the DWI marginal bright signal disappeared, showing no evidence of LTP.
reflect the heterogeneity within an ablation zone. The ongoing technical development will lead to optimization of sequence technique giving a more detailed spatial analysis, especially of the marginal zone that is at risk for LTP. Moreover, detection of small LTP may be improved.

Second, histopathological results were not available for most patients so that RFA success was mostly evaluated on follow-up imaging and clinical parameters (e.g., tumor markers). Long observation period was chosen to overcome this, and to guarantee accurate diagnosis.

5. Conclusion

Unlike treatment of other oncologic tumors, locoregional therapies are mainstay treatments of HCC with RFA becoming widely used. Treatment response assessment using imaging is a key factor in the management of patients with HCC. Conventional MRI is inconclusive in detecting viable tumor in postablation patients.

In conclusion, the present study demonstrates that DWI is a feasible follow-up tool for postablation liver providing more information regarding the viability of treated HCCs and contributing in detection of LTP. Although no significant changes in ADC obtained from the entire ablation zones were detected over time, yet ADC-based evaluation of signal alterations in the periphery of the ablation zone may be helpful in differentiation between LTP and post treatment tissue changes.

Conflict of interest

The authors declare that there are no conflict of interests.

References


