Evaluation of short-term response of high intensity focused ultrasound ablation for primary hepatic carcinoma: Utility of contrast-enhanced MRI and diffusion-weighted imaging

Yuanyuan Zhang, Jiannong Zhao, Dajing Guo, Weijia Zhong, Lifen Ran

Department of Radiology, Second Affiliated Hospital, Chongqing Medical University, No. 74 Linjiang Rd, Yuzhong District, Chongqing 400010, China

Clinical Center for Tumor Therapy, Second Affiliated Hospital, Chongqing Medical University, No. 74 Linjiang Rd, Yuzhong District, Chongqing 400010, China

ABSTRACT

Objective: To explore the significance of contrast-enhanced MRI (CE-MRI) and diffusion-weighted imaging (DWI) in evaluating the short-term response of high intensity focused ultrasound (HIFU) ablation for primary hepatic carcinoma (PHC).

Methods: Thirty-nine lesions in the livers of 27 patients were performed HIFU ablation. Conventional MRI sequences, CE-MRI and DWI were performed 1 week before HIFU and 1 week, 3 months after the therapy, respectively. The short-term responses of HIFU for all lesions were evaluated with MRI.

Results: 28 of the 39 lesions (28/39, 71.8%) showed complete necrosis with no enhancement 1 week and 3 months after HIFU. The apparent diffusion coefficient (ADC) values 1 week and 3 months after HIFU were significantly higher than those 1 week before treatment (p < 0.05). The tumor recurrence was detected in 7 of the 39 lesions (7/39, 17.9%) which had no significant enhancement 1 week after HIFU. On the 3 months follow-up, focal nodules were found on the inner aspects of the treated areas. The ADC values had no significant difference between 1 week before and after treatment (p > 0.05), however, they were significantly higher 3 months after HIFU (p < 0.05). The tumor residuals were detected in 4 of the 39 lesions (4/39, 10.3%) showing enhancement 1 week after treatment and increased size 3 months after HIFU. The ADC values had no significant difference among 1 week before HIFU, 1 week and 3 months after treatment (p > 0.05).

Conclusion: CE-MRI and DWI can be employed to evaluate the short-term response of HIFU ablation for PHC and to guide the patient management.

1. Introduction

Patients with primary hepatic carcinoma (PHC) often have portal venous tumor invasion and advanced liver cirrhosis. Surgical resection in patients without concomitant liver cirrhosis is the treatment of choice with a low rate of life-threatening complications [1], however, which can be performed in only 20–30% of patients with advanced or multifocal disease or inadequate functional hepatic reserve [2,3]. Micro-invasive techniques have been developed for the majority of patients with PHC, to inhibit tumor growth and to improve the life quality of patients [4,5].

High intensity focused ultrasound (HIFU) ablation is one of the extracorporeal local treatment methods which can minimally inva-

© 2010 Elsevier Ireland Ltd. All rights reserved.
not enough to assess tumor response to therapy. Enhanced areas on contrast-enhanced MRI (CE-MRI) presumably represent viable tumor but could also result from post-treatment granulatious issues [18–21]. Diffusion-weighted imaging (DWI) has become a promising biomarker of tumor response to therapy and has been used to assess tumor response after chemotherapy and radiation therapy [22–26]. To the best of our knowledge, the use of DWI in the follow-up of HIFU has not been reported. We hypothesized that DWI associated with CE-MRI can determine the presence of cellular necrosis and be useful in obtaining information about tumor response to HIFU ablation.

2. Materials and methods

2.1. Clinical subjects

The protocol in our study was approved by the ethical committee at the Second Affiliated Hospital of Chongqing Medical University. All patients were informed about this trial and signed consent. Thirty-nine lesions in the livers of 27 patients (5 female and 22 male, ranging 34–73 years with mean age of 56 years) with PHC underwent HIFU ablation from December 2006 to January 2008. PHC included hepatocellular carcinoma (n = 23) and cholangiocellular carcinoma (n = 4). There were 19 patients with single nodule, 5 with two nodules, 2 with three nodules and 1 with four nodules. Totally 25 tumor nodules with a diameter less than 5 cm and 14 between 5 and 10 cm were involved. Pathologic confirmation of the PHC was obtained in 10 cases with needle biopsy, and clinical diagnosis was established in 17 cases by typical MR imaging findings and an obvious increase of serum AFP (Table 1).

All lesions underwent HIFU ablation and underwent conventional plain MR sequences, DWI and CE-MRI at 1.5 T MRI scanner at 1 week before HIFU ablation and 1 week, 3 months after HIFU ablation.

2.2. High intensity focused ultrasound ablation

JC type focused ultrasound tumor therapeutic system (Chongqing HIFU Technology Co., Ltd., Chongqing, China) was used in this study. The therapeutic procedure was guided by real-time US. A D3J US imaging device (Esaote, Genova, Italy) was employed as the real-time imaging unit of the system. The preoperative preparation was conducted according to the principle of surgery. HIFU ablation was performed under general or epidural anesthesia in this study. After suitable anesthesia was induced, the patient was positioned either prone or on his or her right side. Then, the US imaging device was used to establish three-dimensional images of the tumor through moving the integrated probe. The tumor was then divided into several sections. At last, the therapeutic probe treated tumor tissue from the deep to shallow regions of the tumor percutaneously, the targeted regions on each section were completely ablated. This process was repeated section by section to achieve complete tumor ablation [11,17].

2.3. MRI technique

All patients were scanned by a 1.5 T MRI scanner (Signa Excite II, GE Medical System) and an 8-channel controlled-array software coil. All of the subjects underwent routine T1–weighted images (matrix size, 256 × 256; slice thickness, 8 mm; interslice gap, 2 mm; TR/TE, 180/3.0), T2–weighted images (matrix size, 256 × 256; slice thickness, 8 mm; interslice gap, 2 mm; TR/TE, 6000/80), diffusion-weighted images (matrix size, 128 × 128; slice thickness, 8 mm; interslice gap, 2 mm; b value, 400; TR/TE, 2000/50), and breath-hold contrast-enhanced (0.1 mmol/kg IV gadolinium) fat-suppressed T1–weighted images (matrix size, 280 × 160; slice thickness, 4–6 mm; interslice gap, 0 mm; TR/TE, 41.2/0) in the arterial phases, portal venous phases and equilibrium phases.

2.4. MR image evaluation

The images of conventional MRI plain sequences, DWI and CE-MRI were interpreted independently by two radiologists specialized in abdominal MR imaging with 9 and 10 years of experience, respectively. In cases of disagreement, the final decisions were resolved by means of discussion and consensus. An evaluation of image quality was made. The images including artifacts were excluded. Parameters evaluation included the tumor signal intensity, the enhancement characteristic and the measurement of apparent diffusion coefficient (ADC) values. Tissues examined were classified as tumor tissue before ablation, tissue with complete necrosis (region without enhancement 1 week and 3 months after HIFU), tissue with tumor recurrence (lesion with newly emerged enhancement 3 months after HIFU but without enhancement 1 week after HIFU), and residual tumor tissue (enhanced lesion 1 week after HIFU with increased size 3 months after HIFU).

DWI was acquired using b values of 0 and 400 s/mm². ADC maps were calculated using functool software and the imaging workstaion (AW4.1; GE Medical System). ADC values were measured by placing regions of interest (ROIs) on the different tissues. Associated with contrast-enhanced T1–weighted images, we placed the ROIs in the largest sections of the tissues on b0 images and the ROIs were placed simultaneously on the ADC maps, meanwhile avoided the torsion and artifact. The scope of the ROIs should be as large as possible. We measured each interested area five times and meaned the ADC values for further statistical analysis. For the same tissue, the ROIs placement kept almost in the same location in different follow-ups.

2.5. Statistical analysis

SPSS 11.5 software was employed for statistical analysis. ADC values of the tissues before and after HIFU ablation were reported as the mean–standard deviation (mean ± SD). Data in this study were quantitative data with continuous distribution examined by normal distribution. Analysis of variance (ANOVA) was utilized to analyze ADC values of the tissues before and after HIFU ablation. The Fisher LSD test was used for multiple comparisons between groups. Statistical significance was defined as a p-value of <0.05.

3. Results

Twenty-eight of the 39 lesions (28/39, 71.8%) showed complete necrosis, the central region of tumor tissue appeared hypointensity on T2–weighted image, a well-demarcated hypointensity area

### Table 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total of patients</td>
<td>27</td>
</tr>
<tr>
<td>Number of tumor lesions</td>
<td>39</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>22/5</td>
</tr>
<tr>
<td>Age (mean age, interquartile range)</td>
<td>56 (IQR 34–73)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>23</td>
</tr>
<tr>
<td>Cholangiocellular carcinoma</td>
<td>4</td>
</tr>
<tr>
<td>Patients with single nodule</td>
<td>19</td>
</tr>
<tr>
<td>Patients with two nodules</td>
<td>5</td>
</tr>
<tr>
<td>Patients with three nodules</td>
<td>2</td>
</tr>
<tr>
<td>Patient with four nodules</td>
<td>1</td>
</tr>
<tr>
<td>Tumor diameter &lt;5 cm</td>
<td>25</td>
</tr>
<tr>
<td>Tumor diameter 5–10 cm</td>
<td>14</td>
</tr>
</tbody>
</table>

without contrast enhancement on contrast-enhanced T1-weighted image and hypointensity area on DWI compared with adjacent liver tissue 1 week after HIFU. The margin of the treatment region was surrounded by a peripheral thin and regular (<1 mm) rim which appeared hyperintensity on T2-weighted image and progressively contrast enhancement on contrast-enhanced T1-weighted image. Three months after HIFU ablation, no significant abnormal signal intensity and enhancement were detected in the central region of tumor tissue on the follow-up MRI. The peripheral thin and regular (<1 mm) rim was still present at 28% of the periphery of the HIFU-treated area (Fig. 1). In tissues with complete necrosis, ADC values were \((1.19 \pm 0.03) \times 10^{-3}, (2.68 \pm 0.06) \times 10^{-3}\) and \((2.70 \pm 0.06) \times 10^{-3}\) mm²/s 1 week before treatment, 1 week after treatment, 3 months after treatment, respectively. The ADC values 1 week after treatment were significantly higher than those 1 week before treatment \((p < 0.05)\). The ADC values had no significant difference between 1 week and 3 months after treatment \((p > 0.05)\) (Table 2).

Tumor recurrence was detected in 7 of the 39 lesions (7/39, 17.9%), which showed slightly inhomogenous hypointensity on T2-weighted images, no enhancement in the central areas and the peripheral rim enhancement on contrast-enhanced T1-weighted image but hyperintensity on DWI 1 week after HIFU. Three months later, the focal nodule of hyperintensity at the margin of the treated area was detected on T2-weighted image. The corresponding region significantly enhanced on contrast-enhanced T1-weighted image and showed hyperintensity on DWI (Fig. 2). In tissues with tumor recurrence, the ADC values were \((1.12 \pm 0.03) \times 10^{-3}, (1.16 \pm 0.03) \times 10^{-3}\) and \((0.88 \pm 0.05) \times 10^{-3}\) mm²/s 1 week before treatment, 1 week after treatment, and 3 months after treatment, respectively. The ADC values 1 week after treatment had no statistical difference compared with those to 1 week before treatment \((p > 0.05)\). The ADC values 3 months after treatment were significantly lower than those 1 week after treatment \((p < 0.05)\) (Table 2).

The residual tumor tissues were detected in 4 of the 39 lesions (4/39, 10.3%), which showed hyperintensity at the margin of the

Table 2
The changes of ADC values before and after HIFU in different tissues (unit: \(\times 10^{-3}\) mm²/s).

<table>
<thead>
<tr>
<th></th>
<th>Complete necrosis ((n = 28))</th>
<th>Tumor recurrence ((n = 7))</th>
<th>Residual tumor tissue ((n = 4))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 week before HIFU (1)</td>
<td>1.19 ± 0.03</td>
<td>1.12 ± 0.03</td>
<td>1.16 ± 0.04</td>
</tr>
<tr>
<td>1 week after HIFU (2)</td>
<td>2.68 ± 0.06*</td>
<td>1.16 ± 0.03</td>
<td>1.15 ± 0.03</td>
</tr>
<tr>
<td>3 months after HIFU (3)</td>
<td>2.70 ± 0.06*</td>
<td>0.88 ± 0.05*</td>
<td>1.22 ± 0.03</td>
</tr>
<tr>
<td>F value</td>
<td>277.43</td>
<td>15.55</td>
<td>3.98</td>
</tr>
<tr>
<td>p-Value</td>
<td>0.000</td>
<td>0.000</td>
<td>0.058</td>
</tr>
</tbody>
</table>

* Fisher LSD test: \(p < 0.05\), 2 vs. 1.
\(\wedge\) Fisher LSD test: \(p < 0.05\), 3 vs. 1.
\(\dagger\) Fisher LSD test: \(p < 0.05\), 3 vs. 2.
4. Discussion

HIFU ablation has been applied to PHC as an efficient therapy method to prolong survival time. It can transfer energy to target tissues and make the focal temperature rise to over 80 °C inducing coagulation necrosis of tumor tissue and vessel damage [6,7,27–29]. Follow-up is necessary, because the local survivals of cancer cells are still possible after treatment. Imaging plays an important role in the follow-up of PHC treated with HIFU ablation.

The aim of HIFU ablation is to generate an area of coagulative necrosis which is referred to as hypointensity on T2-weighted image and is specifically demonstrated. The conventional MR sequences are helpful in evaluating the response of PHC after HIFU ablation. They could show accurately the changes in tumor size and signal intensity. However, lesions do not substantially decrease in size in short-time follow-up after HIFU ablation. Viable tumors, hemorrhage, liquefied necrosis and inflammatory infiltration could also result in hypointensity on T2-weighted image. It was difficult to judge the viable tumors of PHC after HIFU ablation only by T2-weighted image. The changes in tumor size and signal intensity are not enough to assess tumor response to therapy.

Generally CE-MRI has considered to be helpful in the evaluation of the tumor necrosis, surviving and recrudescing. CE-MRI is a routine in follow-up method for post-HIFU patients. It demonstrates accurately the size, location and coagulative necrosis of the lesions. Our experience confirms that CE-MRI is very useful in the evaluation of HIFU effects. In our study, 28 lesions demonstrated no enhancement in the central region of tumor tissue and a peripheral thin and regular (<1 mm) rim enhancement on contrast-enhanced T1-weighted Images 1 week after HIFU ablation. 3 months after HIFU ablation, no significant changes were detected in the central region of tumor tissues and the peripheral thin and regular (<1 mm) rim was still present in 28% of the HIFU-treated area. Rowland et al. [30] suggested that 1 week after ablation peripheral thin and regular rim enhancement represented the young granulation tissue, which inverted into mature granulation tissue with the passage of time and had no enhancement on contrast-enhanced T1-weighted images. Our experiment confirms the above results. In our experience, loss of enhancement of the treated lesions corresponded to complete tumor necrosis and the peripheral thin and regular rim enhancement was the vascularized inflammatory reaction with granulation tissue surrounding the zone of coagulation necrosis.
Fig. 3. HCC with residual nodule after HIFU ablation. (a) On T2WI before HIFU ablation, the lesion appeared as an area of uneven hyperintensity. (b) On CE-MRI before HIFU ablation, the lesion showed uneven enhancement. (c) On DWI before HIFU ablation, the lesion showed hyperintensity. (d) On T2WI 1 week after HIFU ablation, the residual nodule of hyperintensity at the margin of the treated area was detected. (e) On CE-MRI 1 week after HIFU ablation, the residual nodule of enhancement at the margin of the treated area was detected. (f) On DWI 1 week after HIFU ablation, the residual nodule of hyperintensity at the margin of the treated area was detected. (g) On T2WI 3 months after HIFU ablation, the residual nodule of hyperintensity at the margin of the treated area increased in size. (h) On CE-MRI 3 months after HIFU ablation, the residual nodule of enhancement at the margin of the treated area increased in size. (i) On DWI 3 months after HIFU ablation, the residual nodule of hyperintensity at the margin of the treated area increased in size.

No central enhancement and peripheral enhancement were observed in 7 treated lesions 1 week after treatment. Follow-up images obtained 3 months after HIFU ablation showed nodules at the margin of the treated lesions. Our results suggest all recurrences which occurred at the periphery of the treated lesions might be the residuals, and the adjacent normal liver tissue provided a vascular supply for the surviving tumor cells. Therefore, we should focus on the margin of the treated area. This result suggests that recurrence cannot be judged according to signal intensity characteristics or enhancement patterns 1 week after treatment.

In our study, the residual tumor tissues within 4 treated lesions were detected on T2-weighted image which significantly enhanced on contrast-enhanced T1-weighted image and showed hyperintensity on DWI at 1 week after treatment, the focal nodule corresponded to the residual viable tumor which was detected at the periphery of the treated area. On 3 months follow-up contrast-enhanced T1-weighted image, residual viable tumor showed a progressive increase in size.

The distinction between granulation tissue and viable tumor could not be identified on contrast-enhanced T1-weighted image. Enhancement of granulation tissue could overlap that of viable tumor, which makes the early discrimination of residual and recurrence difficult. Our findings support those of Kuszyk et al. [21]. In addition, CE-MRI is limited to quantify tumor necrosis.

DWI reflects motion of water molecules in tissue. DWI can provide an insight into water movement composition within a tumor and the degree of tumor viability. Viable tumor cells have intact cell membranes that restrict water mobility and cause low ADC values. Conversely, cellular necrosis increases membrane permeability and allows free diffusion of water molecules, which increases the ADC values. These characteristics are used to detect cellular necrosis before size regression occurs. Buijs et al. [24] indicate that DWI and CE-MRI could detect tumor necrosis before tumor size reduction. The change of ADC values is earlier than the change on T2-weighted image, even earlier than histology. DWI has been used to assess the response of PHC to TACE [23,25,26]. To the best of our knowledge, this is the first report about the reliability of DWI in evaluating the response of PHC after HIFU ablation.

The ADC values were employed in this study to conduct quantitative analysis of tumor tissues after HIFU ablation. The ADC values of 28 lesions with complete necrosis after HIFU ablation were significantly higher than those before HIFU ablation (p < 0.05). This can be explained by the increased cell membrane permeability, rupture, and lysis within the necrotic region which increased the extracellular water resulting in increased free diffusion of water molecules outside the cells [31,32].

Signal changes of MRI and alteration of the ADC values in 7 recurrent lesions before and after treatment were examined in this research. T2-weighted image revealed slightly inhomogenous decreased signal intensity and CE-MRI showed no enhancement 1 week after treatment, while DWI kept high signal intensity and ADC values had no significant increase compared with pre-HIFU values (p > 0.05). Three months after HIFU, nodules emerged in the peripheral parts of the lesions. ADC values of the nodules
decreased significantly relative to the values 1 week after HIFU (p < 0.05). Changes 1 week after HIFU may attribute to inadequate dose or time of HIFU resulting in incomplete necrosis of carcinoma, and destruction of carcinoma blood vessels leads to no apparent enhancement. Reversible cellular impairment limits the movement of water molecules, which generates the high signal on DWI and no significantly increased ADC values. Three months after HIFU, the hyperplasia and infiltration of the residual cancer cells in the necrotic areas result in decreased extracellular fluid and limited water diffusion, which causes the significantly decreased ADC values compared with those 1 week after HIFU (p < 0.05).

No significant difference of ADC values among 1 week before treatment and 1 week, 3 months after treatment in residual tumor tissue indicates incomplete necrosis of tumor. Tumor residual should be strongly suspected when no significantly increased post-HIFU ADC is found, which benefits the treatment.

However, it is unlikely that DWI will be the sole predictor of tumor viability after HIFU. DWI has lower-resolution images and is easy to create motion artifacts. A combination of CE-MRI and DWI will be better to assess the therapeutic response of PHC after HIFU and provide more information to guide future therapy.

One major limitation of the present study is that the number of cases was relatively small, further study with a larger number of patients is needed to reach a more convincing conclusion. Secondly, this study lacks histopathologic correlation of the lesions after HIFU ablation. It is difficult to obtain pathologic confirmation in patients who underwent HIFU because most of these patients did not undergo surgery. Due to no histopathologic results in our study, it is hard for us to discuss the exact ADC changes of hemorrhagic/liquefied necrosis and inflammatory infiltration. We will discuss whether DWI is helpful to differentiate the tumor tissues from granulation tissues after HIFU in our further animal study.

In conclusion, DWI and CE-MRI can be used to analyze the degree of tumor necrosis, to timely detect residual tumor and recurrence in PHC after HIFU, to evaluate the short-time response and to guide patient management.

Acknowledgements

This study was supported by the Research Funds of Chongqing Bureau of Health (07–2–121) and National Natural Science Foundation of China (30800262).

References