Diffusion-weighted MR Imaging for Determination of Hepatocellular Carcinoma Response to Yttrium-90 Radioembolization

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Early detection of the response of hepatocellular carcinoma (HCC) to yttrium-90 radioembolization therapy may be important to permit repeat radioembolization or alternative treatment options. Water-mobility measurements with use of diffusion-weighted (DW) magnetic resonance (MR) imaging are useful for noninvasive interrogation of microstructural tissue properties. Findings of DW MR imaging may serve as an early biomarker of HCC response. This study tested the hypothesis that DW MR imaging can detect changes in tumor tissue water diffusion in response to 90Y therapy. In each of six patients with HCC included in the study, tumor water diffusion increased significantly after therapy. DW MR imaging is a promising technique for noninvasive assessment of tumor response to 90Y radioembolization.

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Abbreviations: ADC = apparent diffusion coefficient, DW = diffusion-weighted, HCC = hepatocellular carcinoma, TACE = transcatheter arterial chemoembolization.

HEPATOCELLULAR carcinoma (HCC) is the fifth most common cancer worldwide in men (1) and the fourth leading cause of cancer death in the United States (2). Surgical resection or liver transplantation are the only curative treatment options for HCC, but most patients with HCC are not surgical candidates and therefore receive palliative therapies such as radiofrequency ablation or embolization procedures such as bland transcatheter arterial embolization, transcatheter arterial chemoembolization (TACE), or radioembolization (3–5). Yttrium-90 radioembolization delivers internal radiation to lesions via catheter-directed intraarterial administration of 90Y microspheres (5). Compared with conventional external-beam radiation therapy, selective injection of 90Y microspheres into HCC lesions increases the regional radiation dose(s) to the lesion areas with low levels of toxicity to the normal liver.

Patients with HCC treated with 90Y therapy may be candidates for repeated 90Y administration and/or additional chemoembolization therapies, but the detection of maximum tumor response with use of conventional contrast agent–enhanced magnetic resonance (MR) imaging and/or computed tomography (CT) requires waiting as long as 3 months after therapy (6). Therefore, early noninvasive imaging biomarkers for predicting maximum tumor response to 90Y therapy could greatly benefit patients with HCC. Tumor size changes are the traditional criteria used in the noninvasive assessment of HCC response, but the findings may not correlate with therapeutic efficacy (7). In addition, contrast enhancement after therapy within regions of hemorrhage and edema peripheral to a treated lesion can complicate measurements of tumor size (8).

Water-mobility measurements with use of diffusion-weighted (DW) MR imaging can be useful for noninvasive interrogation of microstructural tissue properties. Recent studies (9,10) have demonstrated that quantitative DW MR imaging may provide sensitive clinical biomarkers for early prediction of radiation and chemotherapy response. In these studies (9,10), increased tumor tissue water mobility after therapy was presumed to correspond to decreased cellularity, cell size changes (ie, shrinkage), and compromised cell membrane integrity. Additional studies have recently validated the use of DW MR imaging for differentiation of viable from necrotic tumor tissues in the VX2 rabbit model (11), and clinical HCC studies (12,13) have correlated quantitative diffusion measurements with tumor necrosis fraction after TACE. The specific cell death pathways induced by TACE and 90Y radioembolization therapies are complex and as yet poorly understood. The former combines localized delivery of chemotherapy followed by
hypoxia-inducing embolic materials, whereas the later delivers local radiation with little embolic effect. On the basis of previous studies evaluating cell death processes during chemotherapy and radiation therapies, it is expected that TACE and radioembolization induce cell death through alternative pathways. Nonetheless, independently of the specific therapy and subsequent therapy-induced cell death pathway, microstructural cell morphology changes and therefore changes in local water mobility. Water mobility changes were predictive of response after irradiation/chemotherapy in brain tumors and after chemotherapy in metastatic breast tumors. Increases in water mobility after TACE have recently been demonstrated in HCC. The tissue destruction should be preceded by microstructural cell morphology changes and therefore changes in local water mobility. Water mobility changes were predictive of response after radiation/chemotherapy in brain tumors and after chemotherapy in metastatic breast tumors. 

### MATERIALS AND METHODS

#### Patients and Radioembolization Technique

In this prospective clinical study, which was approved by our institutional review board, superselective radioembolization (TheraSphere; MDS Nordion, Kanata, ON, Canada) was performed in six patients who had a primary diagnosis of HCC. The diagnosis of HCC was established by fine-needle aspiration or core biopsy and/or noninvasively on the basis of α-fetoprotein levels and previous imaging findings. Patient demographic data including age, cause of lesion, and Child-Pugh classification are given in the Table. None of the patients were deemed candidates for surgical resection. Detailed procedures for the administration of radioembolization with use of a matched-pair analysis imaging coil. The anatomic MR imaging protocol included T2-weighted half-Fourier acquisition single-shot turbo spin-echo and contrast agent–enhanced T1-weighted gradient echo imaging sequences with fat suppression in arterial and venous phases. DW MR imaging was performed with single-shot spin-echo echoplanar imaging during one or more breath-holds with the following scan parameters: repetition time/echo time, 2,500/82 msec; slice thickness/gap, 8/4 mm; bandwidth, 1.5 kHz/pixel; partial Fourier factor, 6/8; nonselective fat saturation; twice refocused spin-echo diffusion weighting to reduce eddy current–induced distortion with b values of 0 and 500 sec/mm².

#### Image Analysis

An Argus image processing workstation (Siemens) was used for MR imaging processing. Apparent diffusion coefficient (ADC) maps were reconstructed from each series of DW images. With reference to T1-weighted contrast agent–enhanced images, regions of interest were drawn to measure mean tumor ADC values. Tumor signal intensity ratios on T2-weighted and contrast agent–enhanced T1-weighted images were also evaluated. We compared mean tumor ADC values and T1- and T2-weighted tumor signal ratios before and after radioembolization with use of a matched-pair t-test with an α value of 0.05.

#### RESULTS

All the patients in this study were able to complete the imaging protocol without complications. A representative contrast agent–enhanced image and corresponding ADC map are shown in Figure 1. In this example, the periphery of the larger tumor (lower portion of the image) showed regions of low water mobility within the viable periphery (dark outer rim on the ADC map), whereas the core of the tumor showed increased water mobility corresponding to a necrotic region. T2-weighted half-Fourier acquisition single-shot turbo spin-echo, contrast agent–enhanced, and diffusion-weighted (b = 500 sec/mm²) images before and after treatment of a patient with left-lobe HCC are shown in Figure 2. HCC conspicuity was relatively low on all images, but by DW MR imaging, previously hypointense regions became hyperintense, reflecting an increase in water mobility.

### Table: Patient Demographic Data

<table>
<thead>
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<th>Patient No.</th>
<th>Age (y)</th>
<th>Lesion Etiology</th>
<th>Child-Pugh Class</th>
<th>Follow-up Interval (d)</th>
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<tr>
<td>1</td>
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<td>Hepatitis C</td>
<td>A</td>
<td>39</td>
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<td>52</td>
<td>Hepatitis C</td>
<td>B</td>
<td>28</td>
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<tr>
<td>3</td>
<td>74</td>
<td>Nonalcoholic steatohepatitis</td>
<td>C</td>
<td>35</td>
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<tr>
<td>4</td>
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<td>B</td>
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pretreatment T1-weighted signal intensity changes are reproducible patterns of T1- and T2-weighted increases were observed in each HCC. ADC of 2.23 (ie, high ADC) suggestive of central necrosis. region (dashed box) illustrates lesion positions (arrows). In b, note the regions of low signal intensity at the tumor periphery (ie, viable tissue) consistent with reduced water mobility and low ADC as opposed to the relatively high signal intensity at the tumor core (ie, high ADC) suggestive of central necrosis.

**Figure 1.** Contrast agent–enhanced posttreatment T1-weighted gradient-recalled echo image (a) and corresponding DW echoplanar imaging ADC map (b) in a 74-year-old patient with HCC. Tumor regions of interest (dashed ellipses) within the magnified liver region (dashed box) illustrates lesion positions (arrows). In b, note the regions of low signal intensity at the tumor periphery (ie, viable tissue) consistent with reduced water mobility and low ADC as opposed to the relatively high signal intensity at the tumor core (ie, high ADC) suggestive of central necrosis.

poor on T2-weighted images, with no significant changes in signal intensity after therapy. Contrast agent–enhanced T1-weighted images typically showed peripheral enhancement corresponding to perfused, presumably viable regions of HCC lesions. For the left-lobe HCC in Figure 2, the contrast enhancement pattern was very similar before and after 90Y therapy, whereas the diffusion-weighted images demonstrated significant water mobility changes within the core of the tumor after therapy. Contrast agent–enhanced and diffusion-weighted (b = 500 sec/mm²) images before and after treatment of a patient with diffuse HCC are shown in Figure 3. Similarly to the previous example, DW images demonstrated significant water mobility changes after 90Y radioembolization.

Tumor ADC increased significantly approximately 40 days after 90Y TheraSphere administration; tumor ADC increased after treatment by a mean of 0.88 × 10⁻³ mm²/sec ± 0.52 (P = .004), with a pretreatment ADC of 1.35 × 10⁻³ ± 0.30 mm²/sec and a posttreatment ADC of 2.23 × 10⁻³ ± 0.32 mm²/sec. Posttreatment tumor ADC increases were observed in each HCC lesion. However, there were no clearly reproducible patterns of T1- and T2-weighted signal intensity changes after 90Y treatment. Pretreatment T1-weighted signal ratio (1.21 ± 0.42) and T2-weighted signal ratio (1.34 ± 0.30) were not significantly different from the corresponding posttreatment T1-weighted signal ratio (1.07 ± 0.37; *P* = .47) and T2-weighted signal ratio (1.40 ± 0.56; *P* = .81). For the six treated lesions, T2-weighted signal ratio increased in three tumors and decreased in three tumors. Similarly, T1-weighted signal ratio increased in three tumors and decreased in three tumors.

Tumor responses were evaluated by means of long-term follow-up MR and CT imaging and measurement of hepatic function and tumor markers (5,6). In long-term follow-up studies, five of the six patients were determined to show a response to the therapy (ie, >50% decrease in the product of the longest diameter and length of the perpendicular diameter of the lesion or >50% increased necrosis as assessed with contrast agent–enhanced CT or MR imaging), whereas one patient was classified as not responsive (6). Although all patients showed increased water diffusion as a result of HCC tissue alteration after 90Y therapy, the posttreatment increase in ADC value of the patient who did not show a response was less than in the other patients. For the patient who did not show a response to treatment, tumor ADC increased by 0.33 × 10⁻³ mm²/sec, whereas tumor ADC increased by 0.84 × 10⁻³ ± 0.42 mm²/sec in the five patients who showed a response. However, the relatively small sample size in this study does not allow testing for statistical significance.

**DISCUSSION**

In this preliminary study, we successfully demonstrated that DW MR imaging can detect changes in HCC lesions approximately 42 ± 16 days after 90Y therapy. All six patients com-pleted the study, and MR imaging studies were performed before and after 90Y therapy. Changes in water diffusion as measured with tumor ADC values on DW MR imaging were statistically significant (*P* < .05), whereas tumor changes established by conventional T1- and T2-weighted MR imaging were not statistically significant.

Intraarterial administration of 90Y is a promising radiation therapy for unresectable HCC. 90Y delivers a significant radiation dose to target regions, with low toxicity to normal liver and with minimal side effects (5). Immediate and long-term follow-up are necessary for determination of any additional treatments necessary to improve prognosis. Traditional criteria used to detect maximum tumor response by conventional MR imaging and/or CT may be ineffective until 3 months after therapy (6). DW MR imaging may provide a surrogate imaging biomarker that noninvasively presages changes in tumor response by means of quantification of tissue water mobility. Our study demonstrated the feasibility of DW MR imaging for the detection of significant increases in HCC tumor ADC values after 90Y radioembolization. DW MR imaging may also offer the potential to differentiate regions of reactive edema from neighboring tumor tissues after 90Y radioembolization. These regions are often represented by high signal intensities on contrast agent–enhanced T1-weighted images, complicating conventional size measurements.

The primary limitations of this study were the relatively small sample size and the variation in delay between therapy and follow-up imaging. A larger systematic study correlating the time course of tumor ADC changes with longitudinal solid tumor response metrics (ie, Response Evaluation Criteria In Solid Tumors [18]) will be necessary to validate DW MR imaging as an early biomarker predictive of HCC response. Another limitation was the lack of histologic confirmation of alteration to tumor cell microstructure after 90Y therapy. Radiation-induced cell death alters tumor cellularity, cell size, and cell membrane integrity. These tissue alterations should lead to decreased intracellular water content (ie, cell shrinkage), increased exchange rates of water molecules between intra- and extracellular populations, and...
corresponding increases in water mobility and ADC. Previous studies (9) have shown increases in tumor ADC after positive response to external-beam radiation therapy. Our study also demonstrated tumor ADC increases after therapy; however, we did not perform pathologic studies to establish alterations that correspond to HCC cell structure. Histologic confirmation can be prohibitively invasive and therefore difficult to obtain during the time course of HCC therapy. However, animal model studies offer the potential to provide such pathologic correlations (11). In addition, 90Y radioembolization has recently been shown to allow downstaging of HCC in a subset of patients, permitting transplantation or resection (19). Future studies in these patients may permit explant pathologic correlation to DW MR imaging water-mobility measurements.

Although the single-shot echoplanar imaging technique is commonly used in clinical DW MR imaging of the

**Figure 2.** Pre- and posttreatment (left column and right column, respectively), T2-weighted half-Fourier acquisition single-shot turbo spin-echo, contrast agent–enhanced T1-weighted gradient-recalled echo, and diffusion-weighted (b = 500 s/mm²) images (DWI) of a 52-year-old patient with left-lobe HCC (arrows). Note the increased water mobility (ie, decreased signal intensity on diffusion-weighted imaging) within the core of the lesion after 90Y therapy illustrated in the magnified region of interest (solid box).
abdomen because of its relative insensitivity to bulk motion artifacts, it may be limited by significant image distortion, chemical-shift artifacts, and reduced spatial resolution, particularly when the imaging field of view is extended, as is necessary for abdominal imaging applications. These limitations have significantly complicated routine clinical DW MR imaging of the visceral organs. Multishot DW MR imaging pulse sequences such as linescan DW MR imaging (20) and DW MR imaging with periodically rotated overlapping parallel lines with enhanced reconstruction (21) have been investigated in an effort to improve image quality and spatial resolution, particularly for neuroimaging applications. Continued development of these multishot techniques may permit high-resolution DW MR imaging of the abdomen.

In conclusion, DW MR imaging can detect increased water diffusion caused by HCC tissue alteration after 90Y therapy. DW MR imaging is a promising technique for the noninvasive assessment of tumor response to radioembolization. Future studies are necessary to correlate the time course of ADC changes with HCC therapy response, and additional technical developments are necessary to improve DW image quality and spatial resolution.

References